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Diseases *of the* Nervous System

Section Two - Supplement

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SYMPOSIUM

on

CHLORDIAZEPOXIDE

A SCIENTIFIC MEETING

Held at the

UNIVERSITY OF CALIFORNIA AT LOS ANGELES
NEUROPSYCHIATRIC INSTITUTE
MEDICAL CENTER

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DISEASES *of the* Nervous System

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Introduction

NORMAN Q. BRILL, M.D.

As serious research workers and teachers, we have a great responsibility to be objective, and immune to the universal tendency to find and believe that which we wish to find and believe. The immensity of the problem of mental illness motivates all of us to want to find a more simple and economical method of treatment, and, therefore, we are especially vulnerable to wishful thinking. I am certain that the scientists and clinicians participating in this Symposium will guard against that, and the extent to which they do, is the extent to which they should be congratulated.

I say this because, in the past, there have been many instances in which this was not the case. I can well remember the optimistic and enthusiastic reports that followed the introduction of insulin shock treatment by Sakel.

Many serious and cautious research workers were convinced that, at last, they had a physiological treatment for schizophrenia that would enable them to empty the state hospitals, and, today, as far as I know, there is not a single hospital in Los Angeles that is using insulin shock therapy.

Doctor Wright published an article in the American Journal of Psychiatry on the drug treatment of 85 psychotic patients. He reported that 50 per cent of them showed decided improvement, and 75 per cent benefited to some extent, and he said: "Patients showing soiling, wetting and destructiveness became more cleanly, less destructive and better able to take care of themselves, and patients given to outbreaks of violence became better adjusted to their environments, and their activities were more easily directed into useful channels."

He said that patients requiring tube feeding took some food voluntarily after two or three days; there was a marked reduction in waste of clothing and bedding from soiling and tearing.

He reported that fewer nurses were required to take care of the disturbed patients once they were treated with the drug.

And one nurse reported, in the article, that "before these patients were treated, we had to struggle with them every morning to get them bathed and dressed. Fights were frequent occurrences. By the time the patients were finally bathed and dressed, we were all tired out from struggling with them before the real day's work had begun."

This article, as some of you may know, was published 31 years ago, and the drug was bromide. It sounds a lot like what we hear today.

In recent years, we have seen a veritable flood of tranquilizers, each of which was produced by expensive and highly praiseworthy research. There is no question that these drugs have a chemical effect on a variety of conditions, including behavior, and there is no doubt that they are valuable in the management of psychiatric disorders.

The question to which we need to direct our attention is: are they any better than drugs which were and are available, and is their effect attributable to anything other than a sedative-like action?

My own belief is that, at this stage of our knowledge about the new drugs, it is not possible to attribute to them anything more than a palliative action on symptoms, as aspirin is for fever. They cannot be expected to resolve underlying conflicts, or deep-seated personality disorders, nor to affect unconscious attitudes any more than aspirin can be expected to cure malaria.

Rauwolfia alkaloids have been used in India for many years but, as far as I know, without any effect on the incidence of

psychoses. And yet, aspirin is a very valuable drug, and the same may be said for the tranquilizers.

We must be careful in evaluating the effectiveness of any drug to distinguish between its effect on symptoms and its effect on the disease. A drug may be very effective in controlling anxiety, but this is not necessarily an indication for its use. Anxiety is one of the major factors that motivates patients to seek treatment. Its presence, therefore, is not only desirable at times, but essential if a patient is going to be motivated to a change.

To prescribe medication routinely to relieve anxiety is like prescribing pain relievers routinely for abdominal pain.

Much has been said and written about the toxic or side effects of the drugs. I'm convinced that they are safe enough. The major danger lies in the tendency to exaggerate their effectiveness, and, generalizations such as: "The Principal Indication for Prescribing Drug A is Anxiety and Tension," which appear in advertisements, can be very misleading. It is one thing to show that a drug can reduce tension, and another to prescribe it.

I have a patient for whom the presence of anxiety and tension is a contraindication for drugs because of her addiction propensity, and yet, half a dozen physicians have prescribed drugs for her simply because she was tense, and, on each occasion, she landed back in the hospital.

I hope that in the subsequent discussions on chlordiazepoxide you will bear in mind some of these considerations.

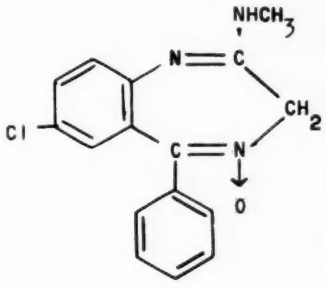
Pharmacology of Chlordiazepoxide (Librium)

LOWELL O. RANDALL, PH.D.*

Chlordiazepoxide** (Librium®) is the first member of a new chemical class of compounds which has shown unique taming effects in animals[1,2] and powerful anti-anxiety effects in human subjects.[3-5] Other pharmacological effects first observed in animals and later confirmed in human subjects include anticonvulsant activity and muscle relaxant effects at low doses with sedative effects at high doses, and appetite stimulating effects. Certain pharmacological effects which were minimal in animal tests were also minimal in human subjects including effects on blood pressure, heart rate, and autonomic nervous system.

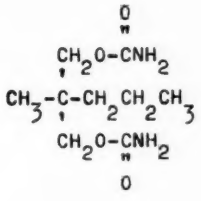
Chlordiazepoxide has been in widespread clinical use for less than two years and it seems of interest at this time to compare the available laboratory and clinical data to see how well pharmacological data in animals correlate with clinical activity. Chlordiazepoxide was first submitted to our pharmacology laboratory in May, 1957. Dr. Sternbach, the chemist who synthesized it, had worked on similar compounds at the University of Krakow, Poland, in 1933. He reactivated the studies at Roche and the first active compound was Ro 5-0690 or chlordiazepoxide.[6] The structure of this compound was not quite clear and only a year after its pharmacological effects were discovered was the current structure finally established (Figure 1).

The first pharmacological data showing the significance of chlordiazepoxide as a muscle relaxant, anti-strychnine compound and spinal reflex blocking agent was obtained by June of 1957 or during the first month after receipt of the compound.[1,2] Data comparing the effects of



CHLORDIAZEPOXIDE

(LIBRIUM)



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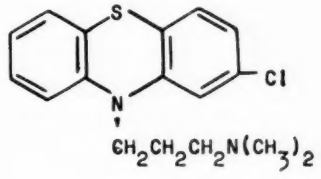
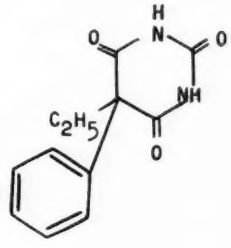


CHLORPROMAZINE



PHENOBARBITAL

Figure 1. Structural Formulae.

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**Chlordiazepoxide is the generic name for Librium which was formerly referred to as methaminodiazepoxide.

chlordiazepoxide with meprobamate, chlorpromazine and phenobarbital are given in Table I.

TABLE I

Depressant Effects in Mice

Compound	Fighting Mice	Muscle Relaxant	Strychnine Convulsions	Ptosis	Hypnotic	Lethal
	ED_{50} mg./kg. p.o.					
Chlordiazepoxide	40	100	87	0	0	720
Meprobamate	300	250	500	300	348	1000
Phenobarbital	80	120	50	120	120	263
Chlorpromazine	20	17	50	5	0	870

The fighting mouse test developed by Tedeschi *et al.*[7] aided in the recognition of chlordiazepoxide as an agent different from other tranquilizers. Pairs of mice were stimulated to fight by electroshocks applied through a grid to the feet. Fighting episodes of mice were prevented by chlordiazepoxide and other tranquilizers (Table I). Chlordiazepoxide abolished the fighting episodes at doses below the muscle relaxant dose whereas meprobamate and chlorpromazine abolished fighting at the muscle relaxant dose; phenobarbital also blocked fighting below the muscle relaxant dose. Chlordiazepoxide was differentiated from phenobarbital by the lack of hypnotic effects at the muscle relaxant dose level.

Strychnine convulsions were also blocked by chlordiazepoxide at the muscle relaxant dose level and this is true also for meprobamate and phenobarbital.

The next step in the pharmacological investigation was the recognition by Heise[1] of the powerful and unique taming effects in monkeys; although the taming effects in monkeys had been claimed for many tranquilizers this was observed only at doses which caused ataxia or sedation with meprobamate, chlorpromazine, phenobarbital and others. Chlordiazepoxide was unique in that the taming effect was observed at a dose only 1/10 as large as that which caused ataxia and sedation. This large safety margin for taming effects in animals has been demonstrated in human trials in which the anti-anxiety effects were readily apparent at sub-ataxic doses. It was this taming effect in monkeys, initially observed in the laboratory, that led to widespread use in human subjects for the anti-anxiety effects.[3-5] The taming effect has been amply confirmed in many species of zoo animals including tigers, lions, dingo dogs and squirrels.[8] This action of chlordiazepoxide is being used by veterinarians in their practice for quieting hard-to-handle animals.

The taming effect of chlordiazepoxide was also demonstrated by Schallek[1,9] in rats which were made vicious by lesions in the septal area of the brain. The dose which blocked the vicious reaction was well below the dose which caused sedation in tests on motor activity in jiggle cages.

The anticonvulsant properties of chlordiazepoxide were recognized by Keith[1,10] in laboratory tests on electroshock and Metrazol convulsions in mice (Table II).

TABLE II

Anticonvulsant Activity in Mice

Compound	Metrazol	Maximal Electroshock	Minimal Electroshock
	ED_{50} mg./kg. p.o.		
Chlordiazepoxide	18	95	150
Meprobamate	150	200	167
Phenobarbital	75	18	90
Diphenylhydantoin	>800	15	600
Trimethadione	400	>80	800

Chlordiazepoxide was recognized to have the broad spectrum anticonvulsant effects of phenobarbital but it lacked the hypnotic effects of phenobarbital. Chlordiazepoxide was much stronger than meprobamate in the anticonvulsant tests. It was active in both electroshock and chemical shock, whereas diphenylhydantoin (Dilantin) was active only in electroshock, and trimethadione (Tridione) was active only in chemical shock. The broad spectrum anticonvulsant activity at sub-ataxic doses

and sub-hypnotic doses has also been demonstrated in human epilepsy.[11]

In a modern adaptation of the classical avoidance experiment, Heise and McConnell[12] have been able to separate the distinctive action of chlordiazepoxide on warning stimuli ("anti-anxiety effect") from its ataxic effects in rats. In animals trained to press a lever to avoid electroshock, it was found that the dose which first produced a decrement in the avoidance response was ⅓ the dose that caused the rat to fail to escape from the shock.

The sequence of events in an experimental trial is shown in Figure 2. In this "trace" classical avoidance, the rats are trained to press the lever during the noise component of a trial consisting of 5-second noise-5-second silent "gap"-shock. The trial terminates when the rat presses the lever, and another trial is presented two minutes later. Drugs may cause failure to press the lever during the noise, (noise response failure), failure to respond during the noise and during the gap (avoidance failure), or failure to respond during the noise, gap, and shock (response failure). Figure 3 illustrates the results obtained in single rats with chlordiazepoxide, meprobamate and chlorpromazine. The curves show the relation between dose and the per cent of trials (measured over a five-hour experimental session) in which there was noise response failure, avoidance failure and response failure.

Although chlordiazepoxide was effective at less than ⅓ the dose of meprobamate, both drugs produced a relatively high proportion of gap responses. The number of gap responses is indicated by the difference between the noise response failure curves and the corresponding avoidance failure curves in Figure 3. The substantial difference between these two curves for chlordiazepoxide or meprobamate shows that after these drugs the rat that failed to press the lever during the noise often responded during the subsequent gap and thus escaped the shock. The distinctive effect of these two drugs on gap responding is summarized in Table III, which shows that with chlordiazepoxide or meprobamate the dose producing noise response failure was less than ½ the corresponding dose that produced avoidance failure. In contrast to chlordiazepoxide and meprobamate, chlorpromazine was much more potent, but produced few gap responses. Table III shows that the dose of chlorpromazine producing noise response failure was only slightly less than that producing avoidance failure. The close correspondence between the noise response and avoidance failure curves for chlorpromazine in Figure 3 indicates that when the rat failed

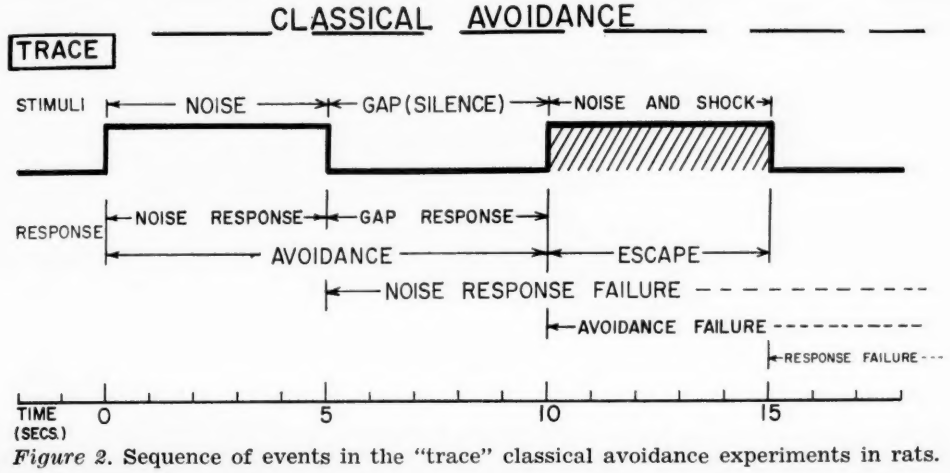

Figure 2. Sequence of events in the "trace" classical avoidance experiments in rats.

to respond during the noise it almost never pressed the lever during the gap, and finally responded only when the shock came on.

Effects of chlordiazepoxide on the spinal cord were studied in cats. The muscle relaxation, evident from the relaxed appearance of cats when suspended by the scruff of the neck, is more powerful than that of meprobamate and phenobarbital, and qualitatively different from chlorpromazine. The latter produces a stiffness of muscle together with retracted hind limbs when held suspended in contrast to the relaxed appearance of Librium-ized cats. The muscle relaxation is attributed to spinal reflex blocking which was demonstrated at low levels. Experiments were performed on the flexor reflex of cats and chlordiazepoxide was found to be more potent than meprobamate and phenobarbital while chlorpromazine was inactive (Table IV).

Schallek has attempted to localize the action of chlordiazepoxide on higher portions of the CNS.[1,13] He found depressant activity on the limbic system (septum, amygdala and hippocampus) at lower doses than on the reticular activating system. Since the limbic system and particularly the amygdala are believed to be concerned with emotional responses, it seems possible that the depressant effects of chlordiazepoxide on these areas could

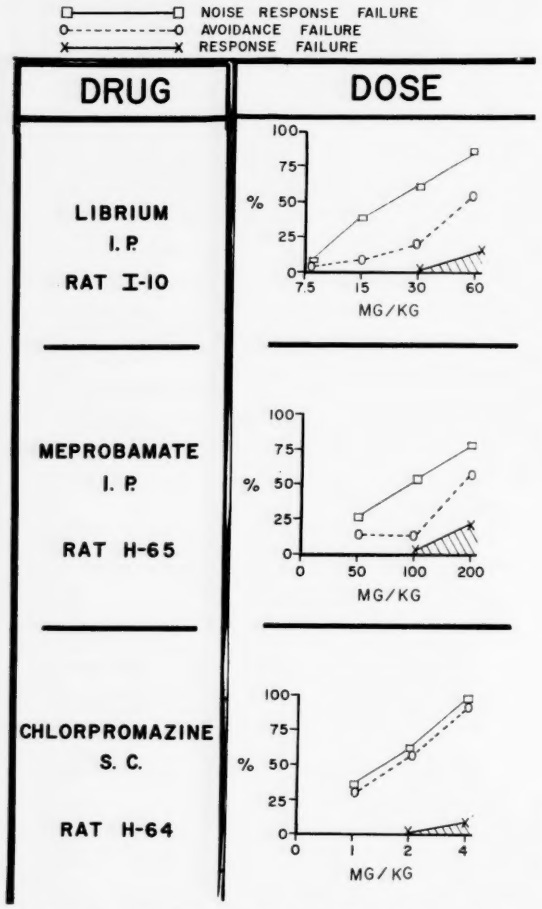

Figure 3. Dose-response curves of the results obtained in the "trace" classical avoidance experiments. The curves show the performance of an individual rat at each dose level of chlordiazepoxide (Librium®), meprobamate and chlorpromazine.

TABLE III

Depressant Activity in Rats

	Chlordiazepoxide mg./kg. i.p.	Meprobamate mg./kg. i.p.	Chlorpromazine mg./kg. s.c.
Trace Classical Avoidance			
a. 25% noise response failure	15	56	0.80
b. 25% avoidance failure	35	130	0.87
c. 10% response failure	46	175	3.2
Septal Lesion	11	95	5.8 i.p.
Locomotor Activity	125 s.c.	240 s.c.	1.8

TABLE IV

Depressant Activity in Cats

Minimum Effective Dose mg./kg.

	Route	Chlordiazepoxide	Meprobamate	Chlorpromazine	Phenobarbital
Muscle relaxation	p.o.	10	50	2.5	50
Spinal reflex block	i.v.	4	50	0	15
Reticular activating system	i.v.	20	40	0.1	1.0
Septum	i.v.	10	20	*	20
Amygdala	i.v.	10	>20	—	—
Hippocampus	i.v.	10	—	—	—

*No effect at 10.

be related to the anti-anxiety effects in human subjects.

Another interesting property of chlordiazepoxide which is unusual among tranquilizers is the appetite stimulating property.[1] Single doses of chlordiazepoxide far below the ataxic dose will cause an increase in food consumption of fasting rats; also in a chronic 90-day experiment a significant increase in weight of treated rats over controls was observed. In similar experiments in dogs, a single small dose increased the food intake of fasted dogs and chronic 90-day treatment caused an increase in body weight.

An advantageous property of chlordiazepoxide is its lack of autonomic blocking effects[1]; moderate doses have no effect on blood pressure or heart rate or on blood pressure responses to carotid occlusion, serotonin, epinephrine, acetylcholine and central vagus stimulation; only high i.v. doses which caused profound sedation would change blood pressure or heart rate.

Considerable progress has been made in studies on metabolism of chlordiazepoxide. A method for determination of chlordiazepoxide in blood and urine was developed by Iliev based on extraction into an organic solvent, hydrolysis with acid and colorimetric determination by the Bratton-Marshall method.[14]

To 2 to 5 ml. of plasma or urine are added 0.5 gram potassium carbonate and the mixture is extracted with 15 ml. of ether by shaking for 30 minutes. After centrifugation, the aqueous phase is discarded; the ether is washed twice with 2 ml. H_2O by shaking for one minute; the ether is dried with 1 to 2 grams of anhydrous sodium sulfate, and 10 ml. of the ether filtrate are extracted with 3 ml. 6N HCl by shaking for 10 minutes. After aspiration of the ether and removal of the traces of ether on a water bath, the tubes are heated for 30 minutes at 125°C.

After cooling, each tube is filled with water to 5 ml. and then 0.5 ml. of a 0.1% sodium nitrite is added; after 3 minutes, 0.5 ml. of a 0.5% solution of ammonium sulfamate is added; after 10 minutes, 0.5 ml. of a 0.1% solution of N(1-Naphthyl) ethylenediamine dihydrochloride is added. The color is read after 10 minutes at 550 μ.

Two micrograms of chlordiazepoxide gave a reading of 0.03 units in the Beckman Spectrophotometer. This represents the maximal sensitivity of the method.

The results in Figure 4 show that after a single i.v. dose of chlordiazepoxide in

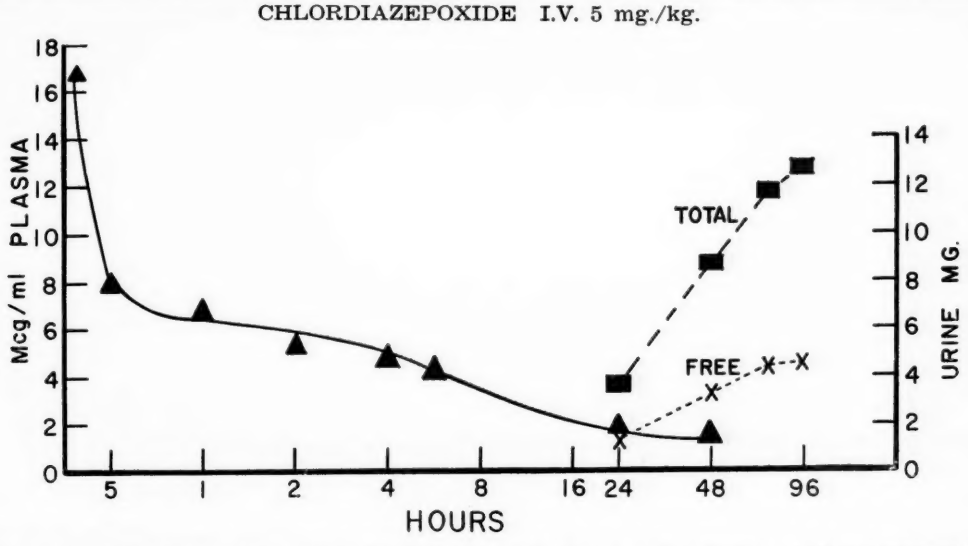

Figure 4. Average plasma levels in 3 dogs given 5 mg./kg. i.v. (left curve) of chlordiazepoxide and average urine levels of free and total (acid hydrolyzed) chlordiazepoxide.

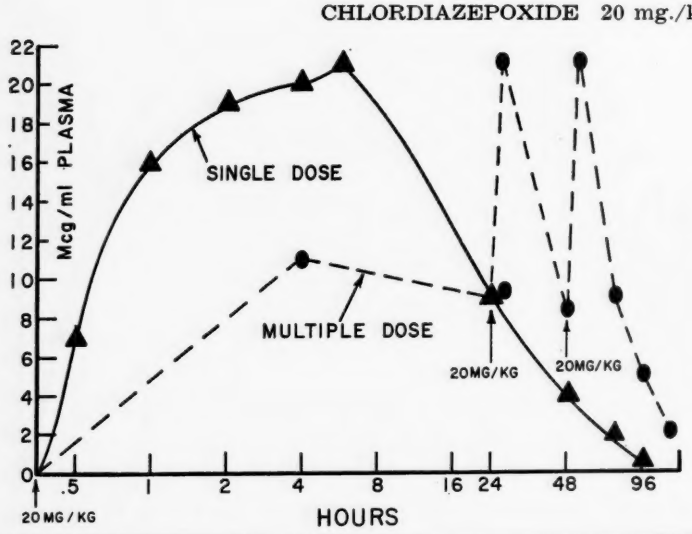

Figure 5. Average plasma levels (microgm./ml.) in 3 dogs given a single dose of 20 mg./kg. orally and average plasma levels of 3 dogs given a dose of 20 mg./kg. orally at 0, 24 and 48 hours (multiple dose).

dogs there is rapid equilibrium with tissues as shown by the rapid decline of plasma levels in the first half hour and then a slow decline over 24 hours; residual amounts are still present after 48 hours. Small amounts of free and combined drug appear in the urine in 24 hours and up to 12% of the administered dose was excreted over 96 hours.

The results in Figure 5 show that a single large dose of 20 mg./kg. of chlordiazepoxide which causes mild sedation induced high plasma levels for 24 hours, and measurable amounts are still present after 48 hours. There was rapid absorption in the first one-half to one hour, but peak levels were not reached until 8 hours. The values declined to about half the peak value in 24 hours. There is considerable variation in the rate of absorption and the peak levels attained. A second series of three dogs received an initial dose of 20 mg./kg., and the plasma levels were 11 microgm./ml. at 4 hours in comparison with the 19 microgm./ml. in the first three dogs, but by 24 hours the values were equal (9 microgm./ml.). A second dose of 20 mg./kg. raised the plasma level to 21 microgm./ml. in 4 hours and then declined to 8 microgm./ml. A third dose of 20 mg./kg. p.o. again caused a rise in 4 hours and a decline by 24 hours to 8 microgm./ml., and measurable levels were present after an additional 48 hours.

These results indicate that a daily dose of 20 mg./kg. induces high blood levels which decline in 24 hours to about the same level after each daily dose. Therefore, the dog is able to metabolize the daily dose without showing cumulative effects on blood level. These blood level data correlate with the fact that a single dose of 20 mg./kg. causes sedation for 24 hours in parallel with the high blood level maintained for 24 hours, but no cumulative effects on either blood levels or degree of sedation were found with successive daily doses.

In studies on human subjects conducted by Brandman,[14] measurable plasma levels were obtained on the very high dose of 150 mg./day. The results in Figure 6 show that the plasma levels rose to 2 to 6 microgm./ml. on the first day and then increased a small amount with successive daily doses of 150 mg. In four groups of patients, continued administration of 25 to 75 mg./day maintained the levels fairly constant. After discontinuing the drug, the plasma levels declined slowly over several days.

The drug was excreted in the urine to the extent of 1 to 2% of the administered dose each day as unchanged drug and 3 to 6% as combined drug which was lib-

erated by acid hydrolysis (Figure 7). Excretion continued for several days at a low level after stopping treatment.

These prolonged blood levels after large doses were confirmed by Schwartz and Koechlin[15] using chlordiazepoxide tagged with radioactive carbon. In these experiments, after a single dose of 15 mg. of radioactive chlordiazepoxide, blood level half-life of radioactivity was 2½ days, while the urines contained active material for 14 days. In rats, blood level and excretion fall-offs were faster (Figures 8 and 9). These facts account for the long duration of action of chlordiazepoxide. It frequently requires several days of treatment of an individual patient until the correct dose is established because the dose has to be adjusted to the rate of metabolism of the drug in each patient. With prolonged treatment at an adjusted dose level in patients or after single large

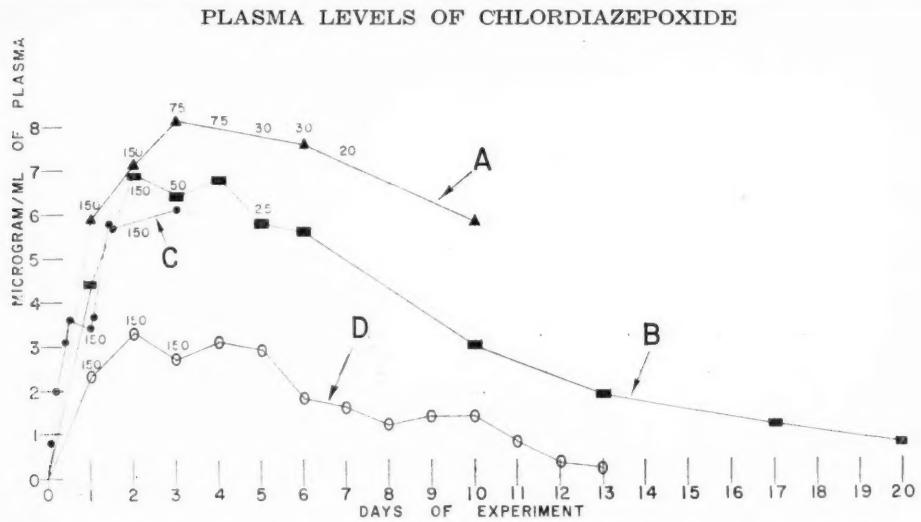

Figure 6. Plasma levels of chlordiazepoxide in human subjects. The daily doses in mg. are given in the curves. The groups had the following number of cases: A-3, B-4, C-6 and D-5.

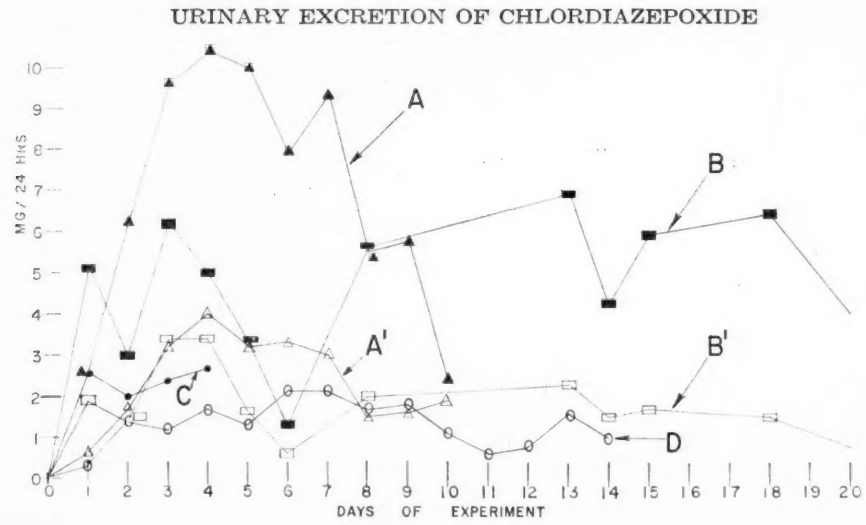

Figure 7. Urinary excretion of free and total chlordiazepoxide in human subjects. The dosage was the same as given in Figure 6. Total drug excretion measured after acid hydrolysis of sample is given in curves A, B, C and D, and the free drug in curves A^1 and B^1.

doses, the effects of chlordiazepoxide are apparent for several days. Excessive doses can lead to ataxia when the body is saturated with the drug. Reducing the dose allows the body to come into equilibrium with the drug at doses which achieve adequate therapeutic effects without inducing ataxic effects.

Chlordiazepoxide is extremely well tolerated in chronic experiments of long duration in rats and dogs. Doses of 50 mg./kg. admixed in the diet have been fed

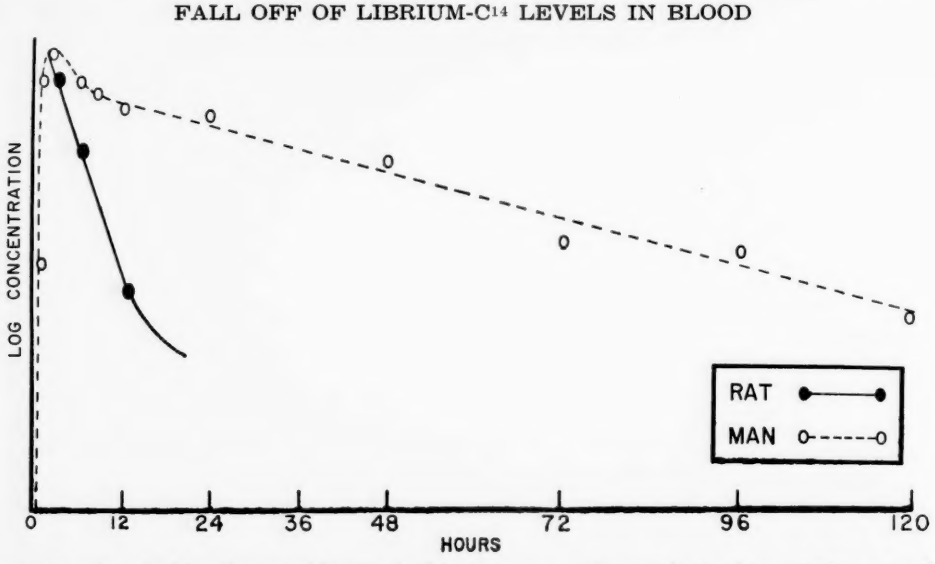

Figure 8. Levels of chlordiazepoxide C^{14} in blood in man after a single dose of 15 mg. and in rats after a dose of 4 mg./kg. The maximum level in man was 1 microgm./ml. with a half-life of 2½ days. In rats the maximum level was 1.8 microgm./ml. with a half-life of 4 hours.

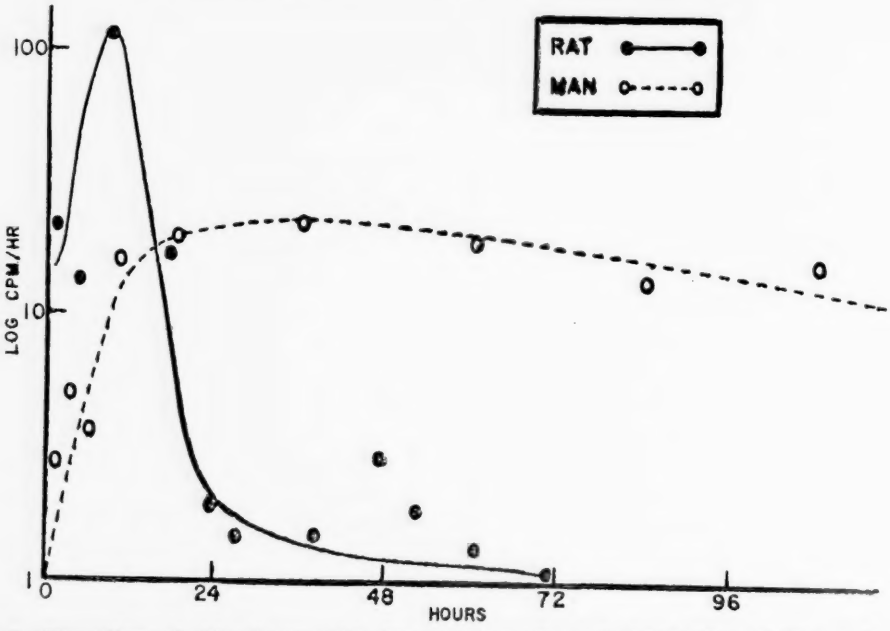

Figure 9. Excretion of chlordiazepoxide C^{14} in urine after administration of 15 mg. in one human subject and 4 mg./kg. in rats.

to rats for over 18 months without causing damage to internal organs. Successive generations of rats in which mothers and offspring were treated with the drug in the diet showed no ill effects.[1,16] Dogs tolerated 50 mg./kg. p.o. for six months. No change in size of gonads, adrenals, thymus, thyroid, pancreas, heart, kidney or other internal organs was found in acute and chronic experiments in rats and dogs.

Summary

The various pharmacological properties of chlordiazepoxide in comparison with meprobamate, chlorpromazine and phenobarbital are summarized in Table V.

TABLE V

Summary

	Chlordiazepoxide	Meprobamate	Chlorpromazine	Phenobarbital
Taming below ataxic dose	+	0	0	0
Taming at ataxic dose	+	+	+	+
Hypnosis at taming dose	0	+	0	+
Autonomic block	0	0	+	0
Appetite stimulation	+	0	0	0
Muscle relaxation	+	+	+	+
Anticonvulsant	+	+	+	+

Chlordiazepoxide has a unique taming effect in monkeys far below the ataxic dose and this quality of a high safety margin between the taming dose and the ataxic dose differentiates chlordiazepoxide from other tranquilizers. The lack of hypnotic effect at high doses distinguishes chlordiazepoxide from meprobamate and phenobarbital. Animals under chlordiazepoxide can be aroused from their sedated state after high doses by gentle prodding. They show ataxia but not true hypnosis on high doses. The lack of autonomic blocking effects differentiate chlordiazepoxide from chlorpromazine which has profound effects on blood pressure, body temperature and autonomic nervous system. The appetite-stimulating effect of chlordiazepoxide is unusual. The muscle relaxation and anticonvulsant effects of chlordiazepoxide are stronger than those of meprobamate and similar to phenobarbital, but chlordiazepoxide lacks the hypnotic effects of meprobamate and phenobarbital. Chlordiazepoxide is rapidly absorbed, and blood levels show a half-life of 2½ days in humans and 4 hours in rats. Only small amounts appear in the urine as unchanged drug.

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Electrophysiological Correlates of Chlordiazepoxide

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Schallek and Kuehn[1] have attempted to localize the central actions of Librium. They performed acute experiments on decamethoniumized cats with bipolar concentric stimulating electrodes placed in anterior and posterior areas of the septum, amygdala and hippocampus,[2-4] and recording from the frontal and occipital cortex. In saline-injected controls, stimulation of the limbic centers gave high amplitude discharges which spread throughout the limbic system, and which usually were characterized by abrupt termination. Duration of discharge following successive stimulations remained constant in the amygdala but progressively increased in septum and hippocampus. Librium injections (10 mg./kg.) caused decreased duration of afterdischarge in septum and hippocampus, as did similar doses of meprobamate, in confirmation of Hunt's work[5] on septal irritability, and of that of Kletzkin and Berger[9] on after-discharge. Librium also caused decreased amplitude of discharge in the amygdala area. Imipramine behaved similarly (cf. also 6): thus, the clinical differences between the three drugs was not differentiated in these studies.

Schallek and Kuehn suggest the possibility that the psychodepressant effects of Librium may be correlated with depression of the amygdala and since it does not affect the midbrain reticular formation associated with consciousness, may provide a neurophysiological correlate for the clinical effects.

King and Meyer[7] presented evidence that the septal region and amygdaloid nuclei may play reciprocal roles in the control of affective behavior, directed toward an integrative center, possibly the hypothalamus which is a critical area for the control of emotional behavior. It is possible that the septum may serve as a control of the hypothalamus and that the amygdala facilitates this diencephalic center.

It is possible that further studies on conscious unrestrained animals with chronically implanted electrodes will reveal such differences, especially if correlated with behavior and learning.[8]

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Chlordiazepoxide (Librium) as an Anti-Convulsant

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Soon after the introduction of chlorpromazine, it was discovered that the phenothiazine type of tranquilizers not only produce EEG abnormalities but clinical seizures as well in susceptible patients. It was even advocated to use such drugs for purposes of EEG activation. This property of the phenothiazines became a hazard when given to epileptics or to those with a low convulsive threshold. Especially in epileptic children behavior disturbances are not uncommon and care had to be taken in selecting a tranquilizer that was compatible with anticonvulsant medication. It is a double advantage if the tranquilizer is also an anticonvulsant.

Since laboratory studies indicated that chlordiazepoxide (Librium®) was such a drug, clinical testing of its anticonvulsant action was carried out in animals (mice) in three kinds of tests:

1) 100 to 125 mg./kg. Metrazol were given to mice, and the dose that prevents convulsion or death in 50 per cent of the animals was determined.

2) 30 milliampere of electroshock were found to produce a tonic extensor response in mice; the dose was sought that would prevent this response in 50 per cent of the mice.

3) In the so-called "minimal electroshock test," mice were given a six milliampere current, producing a partial seizure; the test was repeated 24 hours later with a slightly augmented current, and the dose that would prevent a repetition of the seizure in 50 per cent of the mice was determined.

As can be seen from Table 1, when comparing Librium with phenobarbital, Dilantin and Mesantoin in these experimental seizures, less Librium is needed to prevent a simulated petit mal seizure produced by Metrazol; more than the rest for blocking grand mal, as shown in the supramaximal electric shock test; and less than Dilantin in obviating the experimental psychomotor attack as produced by the minimal electric shock test. If these data can be freely applied to human epileptics, it was expected that Librium would perform well particularly in petit mal and psychomotor seizures.

Librium was given to 43 patients in three groups. Group IA consisted of ten epileptics who had a combination of grand mal and petit mal (7), or petit mal alone (3), who were not previously treated. Seizure incidence for three months was determined and compared with a like period of observation while the patient was given Librium. Dosage started with 0.5 mg./kg., which, in two weeks, was augmented to 1 mg./kg.

Over-all seizure reduction was 50 per cent. Four patients were seizure-free; the two least responsive had a reduction of 20 per cent. In the former, i.e., the seizure-free, were the three who had only petit mal; in the latter were those who had both kinds of attacks.

When the same ten patients were given a combination of Dilantin and Librium, over-all seizure reduction was 75 per cent without any additions to the four who

TABLE I

Anti-Convulsant Activity of Librium Comapared with Phenobarbital, Dilantin and Mesantoin

Convulsion Induced by	Simulating	mg./kg. ED_{50} Phenobarbital	ED_{50} Dilantin	ED_{50} Mesantoin	ED_{50} Ro 5-0690
Metrazol	Petit Mal	75	800	87	18
Maximal Electroshock	Grand Mal	18	15	75	95
Minimal Electrochock	Psychomotor Seizures	90	600	75	150

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achieved complete seizure control when given Librium alone.

Phenobarbital or Mesantoin in lieu of Dilantin failed to improve upon this 75 per cent figure. When 1 mg./kg. was given to children under ten, drowsiness was common. Hence, they fared better on a combined anticonvulsant schedule.

In grand mal-petit mal epilepsy, Librium as an adjuvant is preferable to its use alone, both from the point of view of clinical effectiveness and tolerance.

Group IB consisted of 14 epileptics who had psychomotor seizures alone,[9] or with an occasional grand mal,[5] but presented no behavioral problems in the inter-ictal period. Here the two, three months' periods of observation had to be separated by a two-weeks' interval during which the patients were taken off of their previous medication while Librium was added in a crescendo fashion. The ultimate dose, once again, was 1 mg./kg.

Because in this group Librium was to be compared with a previous medication, the results have to be broken down.

There was no improvement in seizure incidence in four who were taking a Mebaral/Mesantoin combination previously. There was a 25 per cent increase in the frequency of attacks in four who were on a combined phenobarbital and Mysoline regimen. A 25 per cent reduction occurred in six who were on Mysoline alone.

When, however, Mysoline and Librium were combined in the ten who were previously taking Mysoline alone or in combination with phenobarbital, seizure incidence was reduced to 50 per cent, as compared with the frequency on previous medication. One of these patients became seizure-free for the first time, and this has been sustained for the past six months.

The best combination for the psychomotor group, eventually, proved to be Mysoline 500 or 750 mg. combined with Librium, 40 to 60 mg./day.

While the frequency of the attacks decreased, the attack, itself, became longer and less complete. The patients described the change by saying that the attack was "lighter" and that "they lost no control."

Actually, the initial psychosensory phenomena came on as usual, but lasted longer, while the terminal automatism and amnesia element was often entirely absent.

An example that illustrates this is the case of B.S., a 16-year-old male, who had an average of five attacks per month while taking Mysoline (500 mg.), and Mebaral (100 mg.) per day. Increase in either has produced drowsiness. The attack began with a feeling of vertigo, followed by a sensation of vibration and forced thinking. Then, while completely amnestic, he would engage successively in knee slapping, puckering and chewing, and, finally, walking around the room without purpose. The attack lasted, usually, about two minutes.

When Mysoline (500 mg.) was combined with Librium, 40 mg. per day, seizure incidence dropped from 5 to 1 per month. However, the vertigo-vibration-forced-thinking sequence, instead of the usual 30 to 40 seconds, now lasted 1 to 1½ minutes, and knee slapping and other subsequent acts of automatism and amnesia failed to follow. Actually, the whole seizure lasted less than the usual two minutes, but, because the patient was able to recall everything, the illusion of lengthened attack had some basis.

The change in the clinical seizure sequence here, as in many other cases, was accompanied by an alteration of the EEG abnormality.

Thus, the patient described had a large negative spike discharge in the left midtemporal area that spread, in an attenuated fashion, in all directions, homolaterally. Rarely, the opposite temporal lead showed a sharp wave occurring either in synchrony or after a fixed delay with respect to the left temporal spike burst.

When Librium (50 mg.) was administered intravenously, all but the original left temporal spike disappeared. After prolonged Librium administration, in due

time, the majority of the patients showed a similar recession of conducted spike activity leaving the sharply circumscribed original spike untouched.

In conclusion, then, it appears that Librium possesses a blocking quality with respect to the seizure-spreading mechanism for which strongly suggestive clinical evidence is also at hand. A combination of Librium with Mysoline—slightly less with Mesantoin—produced the best anticonvulsant results.

In Group II, Librium was given to ten patients, seven of them under 15 years of age, suffering predominantly from psychomotor attacks who, in addition, showed inter-ictal behavioral anomalies that their usual anti-convulsant medication left uncontrolled. There were, in fact, four of the ten whose behavior improved after each attack, and who were at their worst when seizure-free.

In this group, Librium was added to the medication and placebo control was employed. In six patients, there was improvement, especially in motor restlessness; in three there was no change, and one became worse.

The maximum amount that could be given was 0.5 mg./kg., owing to the drowsiness produced by larger doses. Placebo was alternated with Librium every two weeks and, in all but one, the difference was noted.

It was hard to reach a conclusion in this group. Currently, a larger series of such patients are in the process of being tested in order to determine what those who responded favorably had in common. It appeared that motor restlessness was easier to control than emotional outburst. There has been, as yet, no time to assess these cases as regards the EEG.

In Group III, Librium was given to nine patients—children under 16 years—who, without actual seizures or specific seizure records of the EEG, suffered from behavior disorders, more often periodic than continuous in character and who, in addition, showed some definite EEG abnormality, mostly occipital and posterior temporal sharp wave dysrhythmia. Here, Librium alone was given, alternating with placebo every two weeks. The dosage was 0.5 mg./kg. for two weeks, and raised to 1 mg./kg. subsequently. In six of the nine children, there was decided improvement. However, in three out of nine cases, the difference between Librium and placebo was not picked up.

Interestingly, reduction in attention scatter and resultant improved school performance were noted, even in those whose degree of improvement in explosive behavior was modest. The EEG showed no improvement in those who could be retested up to the present time.

This report does not cover the effect of Librium on the normal EEG pattern. Highly synchronized, monorhythmic fast patterns, so typical of barbiturates and many other sedatives, including meprobamates, rarely failed to appear after one week's administration when 1 mg./kg. was given. On the other hand, rapid intravenous Librium administration failed to show it in two hours, which may be due to insufficient dosage.

Certainly, we have not seen a slow shift in the background alpha range, delta waves, focal slowing which were reported in the literature when testing phenothiazine-type tranquilizers.

In summary, this preliminary survey attests to the anticonvulsant properties of Librium in humans. It has, in our hands and in this selected material, produced better results when it was given in combination than alone.

It has a special effect on both the clinical and electrographic pattern of psychomotor epilepsy, a fact which has important theoretical implications. We have not had a chance to verify this special effect in other focal seizures, where it may well apply also.

In the behavior disturbances of epileptics, it shows promising results that warrant further study with more precision in patient selection.

"Startle" Epilepsy Treated with Chlordiazepoxide (Librium®)

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Introduction

Epilepsy is a sporadic and paroxysmal phenomenon and the factors which produce seizures at any given time are usually unknown. Rarely, a seizure may be produced as desired in a patient, by certain appropriate precipitating factors. The stimuli involved are varied, and the seizures produced by them have been referred to by the term "reflex epilepsy."

Hall[1] introduced the concept of reflex epilepsy in 1833. He divided epilepsy into centric and eccentric types. Eccentric types included those seizures induced by and originating from peripheral stimulation, while centric seizures originated within the central nervous system. Since Hall's time, clinicians have been familiar with the fact that, in occasional cases, certain peripheral sensory stimuli could produce seizures.

Jackson,[2,3] in 1886, described two patients in whom seizures were induced by sudden, unexpected touching of the head. Gowers,[4] in 1901, reported on patients in whom seizures could be produced by light, voluntary motion, and the abrupt tension produced by obtaining tendon reflexes. Seizures induced by stimulation of skin, subcutaneous structures and mucous membranes have been described by Rosenhain,[5] Holmes,[6] Critchley[7] and others.[8-13] Provocation of convulsive seizures by acoustic,[4,7,14-18] optic and photic stimuli[6,7,19-22] has been described by numerous authors. Allen,[23] in 1945, reported 21 cases in which seizures could be induced by either loud noises, gentle stroking of certain areas of the body or by bright lights. Other cases have been noted in which music[24,25] and reading[26] were precipitating influences. Thus "tactile," "photogenic," "audiogenic," 'musicogenic" and "reading" epilepsies were established as clinical entities.

However, what at first sight had appeared to be a simple stimulus-response mechanism turned out, on closer study, to be much more complex. Critchley[7] emphasized the multiplicity of factors operating in "reflex" epilepsy and in some cases similar to the one described by Jackson; he presumed that the seizures were not responses to simple sensory stimuli, but rather to a successfully elicited "startle" reflex, the latter being evoked by an auditory or tactile stimulus.

Lennox and Lennox[27] stated that in many cases of "reflex" epilepsy surprise is an important, if not essential, element of the reflex. They cited a patient[18] who would have a generalized convulsion if a pan were dropped behind him, but not if he saw it dropped.

Peet[17] and his associates emphasized the importance of startle in four cases where stimuli, in order to be effective, had to surprise or startle the patient.

Penfield and Jasper[28] also pointed out that, in some cases, sound tended to produce attacks only when it was so sudden as to produce a startle reaction and that this reaction might be the primary factor. They suggested that such seizure induction could therefore be more appropriately called "startle precipitation."

In this manner, the clinical complex of "startle" epilepsy has been described, discussed and developed in the neurological literature.

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The case presented is one of "startle" epilepsy and, though but a single case, it is of sufficient interest to justify detailed report, not only because exact observations on "startle" seizures are rare, or because interesting electroencephalographic findings are demonstrated, but, particularly, because of the apparent therapeutic effects obtained with Librium, where other forms of therapy had failed.

Case Report

The patient, a girl, nine years old, has been treated at the University of California Medical Center since November 7, 1960.

The family history was irrelevant with no epileptic or epileptoid heredity. The patient, a first born, was the product of a normal, full-term pregnancy and uneventful labor of six hours. Her physical condition was normal at birth, her weight being 6 lbs. 11 oz.

The patient's state of good health continued until she was 18 months old. At that time she began having seizures which always occurred during sleep. She would awake as if from a nightmare, crying and screaming, her face pallid, but sweating profusely. She would stare ahead, grit her teeth, clench her fists, and manifest jerking movements of the head and extremities. There was no loss of sphincter control, tongue biting, or salivation. She seemed to be aware of her environment, appropriately answering "yes" or "no" to questions. The spells occurred 3 to 4 times a week and were followed by weakness, an inability to walk, and deep sleep.

During the next three years, it was noted that in addition to her spells during sleep, she would have several brief episodes each week with sudden weakness in the lower extremities, at times momentarily dropping to the ground. In September, 1953, an electroencephalogram was reported as normal as were x-rays of the skull. She was treated with Dilantin and phenobarbital, with constant adjustment of medication which provided no seizure control.

In 1954, when the child was three years old, her nocturnal sleeping spells ceased and she began to have seizures of a different type. With these, she would, in a single movement, suddenly fling her arms upward and outward and draw her legs up, abruptly falling to the ground, with loss of consciousness for about 10 seconds. She then revived and appeared normal. Close observation revealed that these spells were always associated with the child's being startled by various means: a telephone suddenly ringing, a person unexpectedly shouting at her, the sudden appearance of a Halloween mask, an abrupt slap on the buttock.

Over the next few years these seizures increased in frequency, occurring as often as 12 times a day, and because of the difficulty in controlling them, the patient was hospitalized at the Palo Alto Clinic in July, 1956. A pneumoencephalogram showed brain stem and cerebellar atrophy. No specific abnormal neurological signs were noted.

All medications were then discontinued but her convulsions persisted and if anything increased in frequency. She became unsteady in her gait, lethargic and unresponsive. At least 20 anticonvulsant medications were tried over the next 4 years, singly and in various combinations with no notable effect.

In August 1960, the patient's mother observed, in addition to the "startle" spells, the onset of continuous twitching and jerking of the left arm, shoulder and, occasionally, the left face and leg. This persisted almost constantly for 6 weeks, during which time the child continued to become more unsteady and ataxic, more uncooperative and lethargic. In September 1960, she was again hospitalized at the Palo Alto Stanford Hospital, where the observed prolonged jerking of the left hand, arm, shoulder, face and leg was described as a state of "epilepsia partialis continua." X-rays of the skull were normal, as was a glucose tolerance test. The diagnosis was myoclonic epilepsy, and further deterioration was anticipated.

On November 7, 1960, the patient was admitted to the University of California Hospital. At that time, she was being treated with Mebaral, 30 mg., t.i.d., and Peganone, one tablet, b.i.d. The continuous jerking of the left side of the body had ceased and the patient was now experiencing only her usual "startle" spells. These occurred approximately 3 to 4 times per day.

She had numerous seizures during the first 2 weeks of hospitalization, all of which were essentially the same, occurring with unexpected auditory, visual, or tactile stimuli: a sudden loud noise, the abrupt, though silent, entrance of a nurse, the unexpected bite of her pet turtle.

Immediately following a startling stimulus, the patient would jerk her head forward, hunch her shoulders and trunk and fling her arms upward and outward, simultaneously stiffening her body and drawing her legs upward. The response closely resembled a markedly exaggerated Moro or startle reflex. This was immediately followed by a period of unconsciousness lasting from one half to two

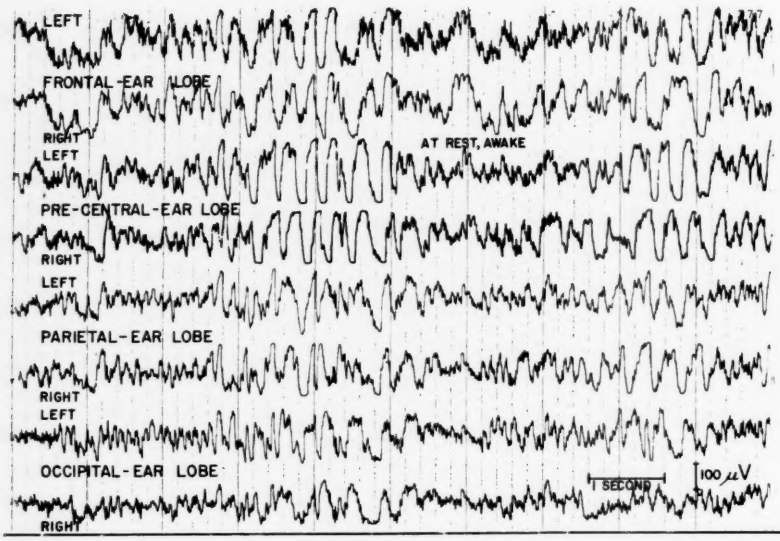

Figure 1. EEG at rest with usual anticonvulsant medications. Record characterized by high voltage generalized and paroxysmal dysrhythmias of non-specific and atypical spike and wave types.

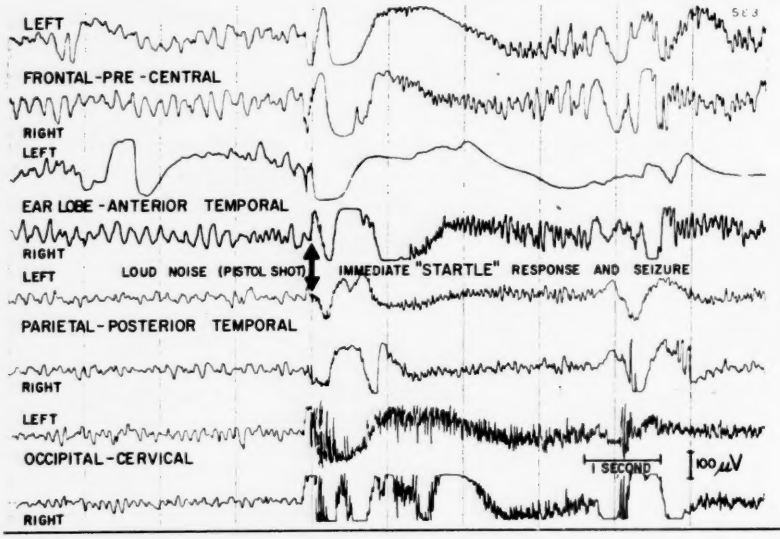

Figure 2. EEG (resting, usual anticonvulsants) with blank-pistol shot producing clinical "startle" seizure manifested in the record by medium-high voltage spiking activity.

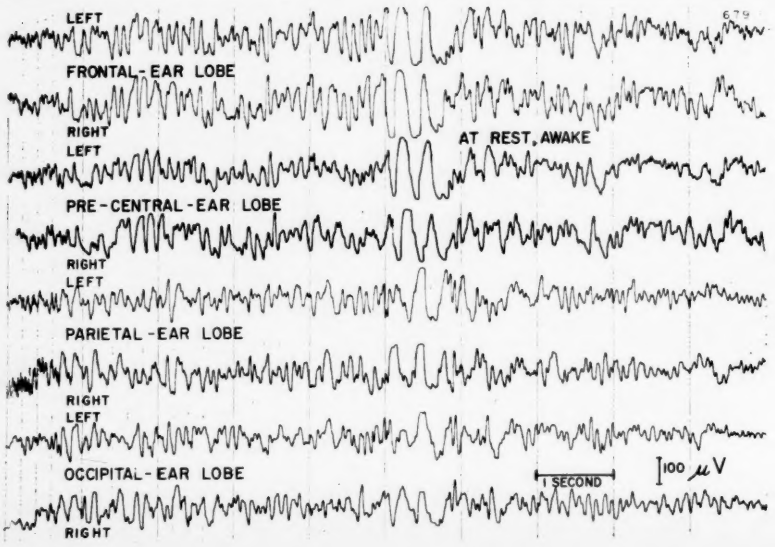

Figure 3. EEG at rest with no therapy (5 days). Record shows generalized, paroxysmal dysrhythmias of non-specific and atypical wave and spike types.

minutes. She then would awaken in an agitated, confused and weeping state, which lasted for a few minutes. With her spells, diffuse erythematous splotching of the skin which faded within 10 minutes, was consistently noted over the face, trunk, and extremities.

Examination on entrance to the hospital revealed a well-nourished child of normal growth. She was extremely uncooperative, hostile, and, at times, lethargic. Her speech was slurred. She refused to stand or walk, being fearful of having a spell and injuring herself in a fall; awake or asleep, she constantly wore a protective helmet, and spent most of her time in bed or in a wheelchair. General examination disclosed no abnormalities. The blood picture and urinalysis were within normal limits.

Neurological examination revealed only mild nystagmus to right and left lateral gaze, generalized mild weakness and an unsteady gait. Reflexes were normally active and symmetrical, but during and immediately following seizures, bilateral extensor responses were obtained. The sensory sphere was intact.

Because the patient was subject to seizures when she was startled, it was felt that they could be controlled primarily if one could reduce the susceptibility to startle stimuli. What was needed was an agent with a specific calming and tension-reducing effect and, additionally, with anticonvulsant properties. Librium appeared to satisfy these criteria. Its calming effects were well known, and its anticonvulsant properties have been demonstrated in animals,[29] and in humans by Kaim and Rosenstein.[30,31] Accordingly, a study was performed to determine if treatment with Librium could control the patient's epilepsy.

Study

Serial EEG's and motion picture films were obtained and startle stimuli (consisting of the firing of a blank pistol) applied: (A) with the patient on her usual anticonvulsive regimen; (B) with no medication; (C) with the patient receiving Librium, 5 mg., t.i.d., and (D) with Librium, 10 mg., t.i.d.

(A) During the first week of hospitalization, with the patient taking Peganone, 1 tablet, b.i.d., and Mebaral, 30 mg., t.i.d., a series of three EEG's were disturbed by high voltage generalized and paroxysmal dysrhythmias of non-specific and atypical spike and wave types and were compatible with a convulsive susceptibility (Fig. 1).

During the third of this series, the unexpected firing of a blank pistol on three occasions produced three characteristic "startle" seizures manifested in the EEG record by medium to high-voltage spiking activity (Fig. 2).

(B) Over a period of one week, the patient's anticonvulsants were gradually decreased until she was on a regular diet with no medications. She continued to have 2 to 3 "startle" spells each day, with no change in intensity. The EEG at rest, with no therapy for five days, was similar to the initial studies, again showing generalized and paroxysmal dysrhythmias of non-specific and atypical spike-and-wave type (Fig. 3). During the EEG, in two attempts, blank pistol shots succeeded each time in producing "startle" seizures (Fig. 4).

(C) Following this, the patient was given Librium, 5 mg. t.i.d. After one week, the resting EEG showed considerable improvement, with only mild irregular slowing being evident (Fig. 5). During the recording, three blank pistol shots produced *no* clinical "startle" seizures and no change in the EEG pattern beyond that produced by movement artifact (Fig. 6).

One attempt did produce a brief loss of consciousness without the typical "startle" seizure response. The EEG, however, showed a seizure activity consisting of atypical spike-and-wave activity (Fig. 7). During that week only one questionable seizure was reported.

(D) The patient's medication was then raised to 10 mg., t.i.d. After one week, the EEG at rest was within normal limits for a 9-year-old child (Fig. 8). In three attempts pistol shots produced no "startle" seizures and no change in the EEG (Fig. 9). The patient had no seizures during the ten days while on 10 mg. of Librium, t.i.d. In addition, she became more cooperative and her behavior improved considerably. The neurological examination was normal.

The nature of her seizures and the responses to "startle" stimuli before and after treatment with Librium are demonstrated in Fig. 10.

Follow-Up

The patient was discharged on December 6, 1960, on the dosage of 10 mg., t.i.d. Three days thereafter, and for the following week, she began to have single daily spells with loss of consciousness which consistently occurred in the morning. It was found that the patient arose at 6:30 a.m. each day and was not given her initial dosage of Librium until one and a half to two hours later. Her dosage was increased to 10 mg., q.i.d., and the patient's mother was instructed to give her the medication immediately upon arising. No seizures were reported until January 5, 1961, when she had one spell. Her parents described

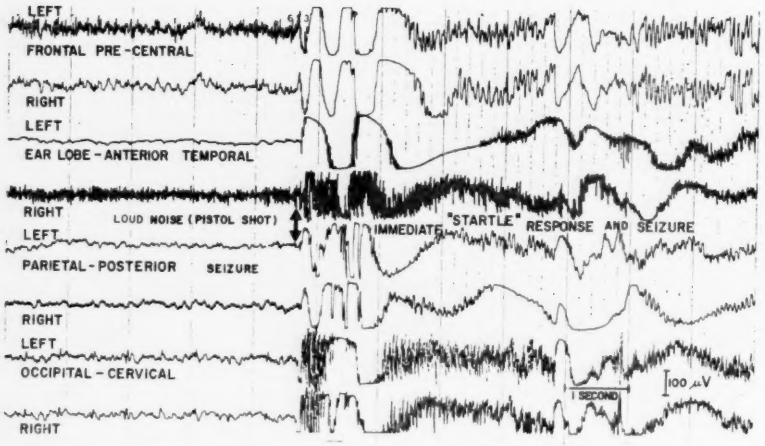

Figure 4. EEG (no therapy, 5 days) with pistol shot producing "startle" seizure manifested in record by continuous spiking activity.

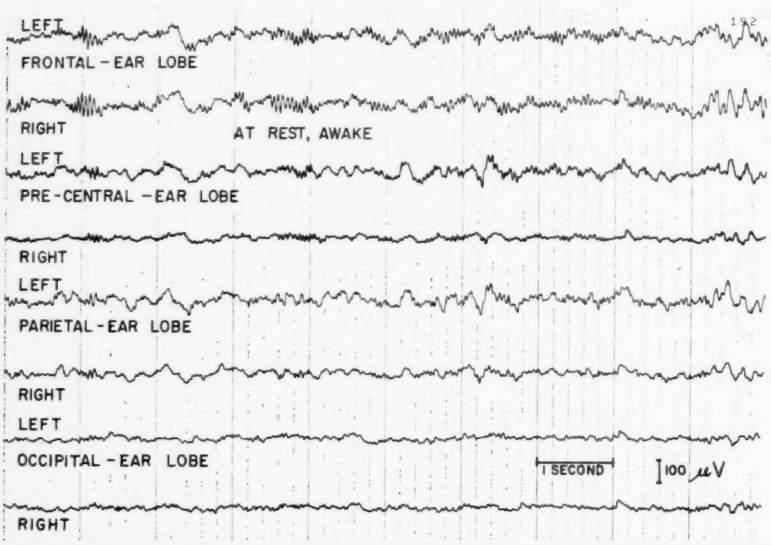

Figure 5. EEG at rest after treatment with Librium (5 mg. t.i.d.) for 1 week. Record shows considerable improvement, with only mild irregular slowing evident.

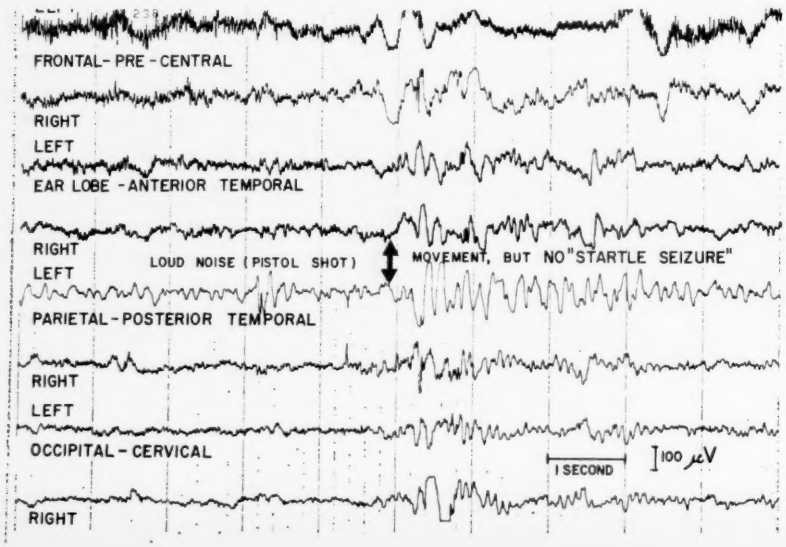

Figure 6. EEG (Librium 5 mg. t.i.d., 1 week) with pistol shot producing brief movement but no "startle" response and seizure. Record shows movement artifact, but no change in EEG pattern.

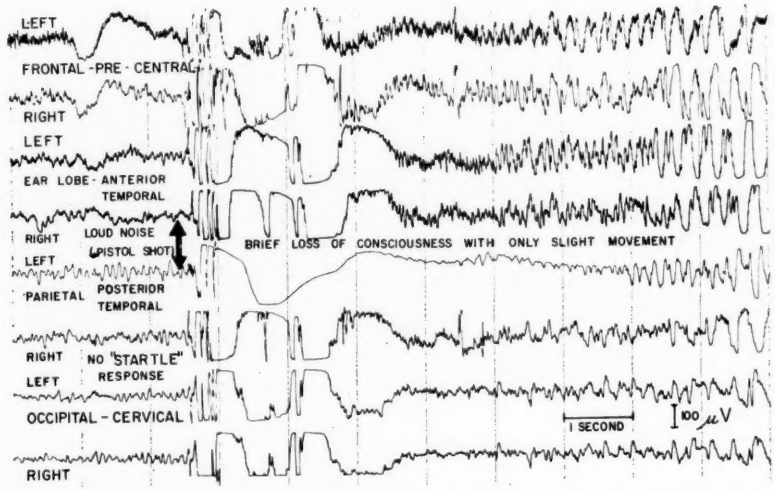

Figure 7. EEG (Librium 5 mg. t.i.d., 1 week) with pistol shot producing brief loss of consciousness without typical startle response. Record shows spiking and a typical spike plus wave activity.

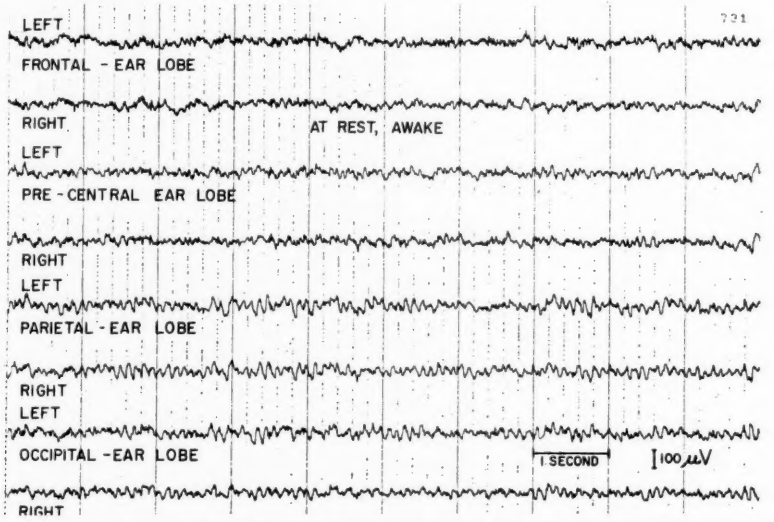

Figure 8. EEG at rest after treatment with Librium 10 mg. t.i.d., for 1 week. Record is within normal limits.

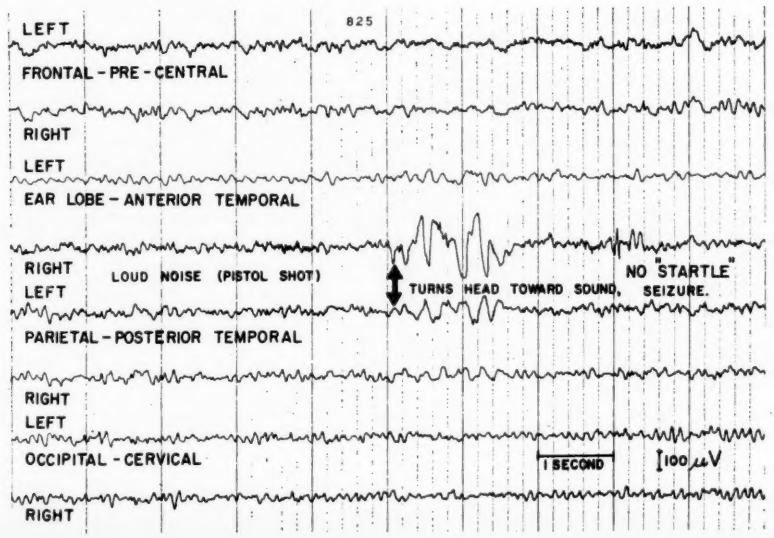

Figure 9. EEG (Librium 10 mg. t.i.d., 1 week) with pistol shot producing no overt abnormal response, no "startle" seizure and no change in the EEG.

her activity as having improved remarkably. She was able to walk properly, played outdoors normally and was attending school. During the entire course of her treatment, no side effects were observed.

Discussion

The startle mechanism is probably related to arousal, and the physiologic mechanisms involved must have free connections with all afferent inflow, as well as the cortex. This suggests that a primary, deep, central structure is involved, probably located in the brain stem or midbrain. The startle seizure then may consist of pathological exaggeration of the normal reflex, which, in a susceptible individual, facilitates a rapid diffuse spread of discharging activity from the deep central structure. If this is so, then the therapeutic effect obtained in this patient may have occurred in two ways: First, it has been reported that Librium has the effect of blocking alerting responses to sound and other stimuli. In our patient this may have reduced the effect of the primary stimulus, resulting in a dampening of the startle reflex; and secondly, the normalization of the EEG at rest suggests that Librium has a general effect of blocking the spread of abnormal activity.

Conclusions

In view of the fact that only a single case has been observed over a relatively short period of time, any conclusion concerning this study must, necessarily, be regarded as solitary and tentative.

Therefore, with respect to our patient, our observations thus far indicate that Librium was effective in limiting the frequent "startle" seizures which had remained relatively intractable to numerous other forms of treatment. In addition, with Librium, the electroencephalogram showed considerable improvement. Thus, the present study, though severely limited, supports the suggestion that Librium, or one of its derivatives, may become a useful agent in anticonvulsant therapy, and particularly in those ("reflex") epileptic

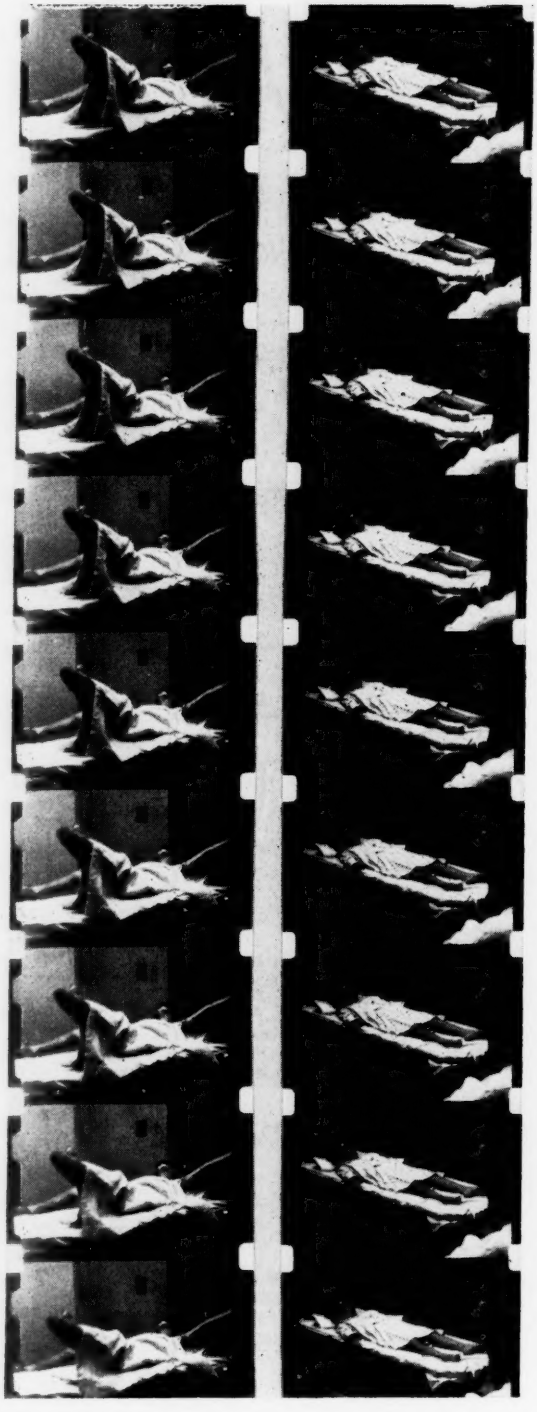

Figure 10A. *Figure 10B.*

Fig. 10. A. Moving picture film of patient, with usual medications, showing "startle" seizure produced by "blank" pistol shot. B. Moving picture film of patient after treatment with Librium, 10 mg., t.i.d., for one week. Pistol shot does not produce a "startle" seizure.

disorders in which peripheral stimuli facilitate the diffuse spread of convulsive activity from deep, central structures.

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Chlordiazepoxide in Clinical Practice

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Chlordiazepoxide has come to be one of the more widely used of the antianxiety agents, and its evaluation by this symposium is timely and will serve to assist in an understanding of this new psychochemical. Fourteen months ago, a meeting on Ro 5-0690, as it was called at that time, was held at the University of Texas. Some of the papers presented were preliminary, and the conclusions were tentative. Since then, some of the contributors at that meeting have reported on larger series of patients given the drug for longer periods of time. In addition, many new reports are available to us now. Most of you in the audience have personal experience with chlordiazepoxide. Therefore, a wealth of clinical impressions is available to be ordered and understood. Let us analyze the information that has accumulated since the Galveston meeting in those patients without major psychiatric disease.

It is difficult to visualize a medical or surgical patient who does not arrive at the physician's office with some measure of fearfulness, or whose ego mechanisms have not already dealt with this emotion. Indeed, it is concern and apprehension which usually prompts his visit to the doctor. Such a response to a disorder of body function or structure is quite appropriate. It motivates him to seek out the physician, to cooperate with the treatment, and to endure the discomforts and indignities of some of our diagnostic procedures. Of course, an emotional response of this magnitude should not be treated.

If the patient's state of tension is producing symptoms, evoking a painful dysphoria, or rendering the patient ineffective in his interpersonal affairs, it requires management. That management may consist of reassurance, explanation or encouragement, or it may be all of these, plus psychochemotherapy.

All illness could be divided into three subgroups, although I will be the first to admit that the boundaries are indistinct. These are the organic diseases like diabetes, congestive heart failure and emphysema. Anxiety is known to precipitate or intensify many of these conditions. Then, there are those called functional; malfunctional might be a better word. Anxiety is an important factor in the etiology of these psychophysiologic reactions. Occupying a mid-position are the classical psychosomatic syndromes like peptic ulceration and hypertension. Here the interplay between the emotion and the end organ is multiple and complex. Correction of the disturbance may tend to disrupt the feedback mechanisms between the periphery and the brain, thereby inducing symptom relief. I do not happen to adhere to the notion that amelioration of symptoms will often result in new, and more disruptive disorders. On the contrary, relief of pain, tension or depression generally permits the organism to reestablish a better adaptive level of behavior.

A safe, tension-reducing agent is essential in present-day practice of medicine. Judiciously used, it can assist in the management of the three classes of patients noted above. The drug under consideration is supposed to be of this order.

Indications:

Librium has been used with some success as an adjunct in the treatment of a variety of illnesses in almost every medical and surgical sub-specialty. This seems to be due to its capacity to modulate feeling tone rather than for any more specific action on the disease process. Alterations in the subjective response to the disease process can be sufficient to alter the underlying disorder. It is for this

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reason that angina, hypertension and post-myocardial infarction states, for example, are assertedly favorably modified by Librium.

Recently Hirshleifer[1] asserted that it is superior to amine oxidase inhibitors or nitrates in its anti-anginal effect. In 34 patients, Librium was rated as giving complete relief in 24, and almost complete relief in five. Unfortunately, comparative EKG's under measured performance loads were not done prior to and during treatment. Gratifying relief in two patients with postmyocardial shoulder-hand syndrome, and in seven of nine patients with arteriosclerotic head noises were also reported.

The capacity of chlordiazepoxide to control disturbing affects has also prompted its use as a preoperative and postoperative agent for anxious obstetrical, gynecological and surgical patients. As a relaxant for gastrointestinal psychophysiological complaints like spastic colitis and esophageal-gastric dysfunction, the drug appears to be satisfactory.

Dermatologists have employed the agent for its tension-relieving property in the dermatoses which have a psychological component. Robinson[2] attempted to compare chlordiazepoxide with a barbiturate, buclizine and meprobamate for two to five week courses for psoriasis, lichen planus, seborrheic and atopic dermatitis, anal and vulvar pruritus. His patients preferred Librium to any of the other three drugs. They expressed a sense of well-being in addition to its symptom-relieving property. For itching, an antihistamine had to be added, Librium alone was not antipruritic.

Its muscle relaxant properties have been insufficiently examined to make a firm statement in this regard. Likewise, Librium's ability to potentiate certain drugs is also open to question. One report points to an enhancing action on narcotics, and recommends its usefulness in de-addiction. Bowes[3] feels that it does not potentiate alcohol, and Hines[4] quoting an unpublished paper of Rosenstein and Silverblatt also speaks of a lack of potentiation of narcotics in cancer patients.

Nor am I yet convinced of Librium's value as an anticonvulsant. In one small study Kaim and Rosenstein[5] found a decrease in seizure frequency, normalizing of the EEG pattern and increase in the Metrazol threshold. They claimed that for most of their nine patients Librium was more effective than the prior anticonvulsant therapy. The Houston State Psychiatric Institute group[6] had one patient on Dilantin who went out of control and had many grand mal seizures when Librium was added. We also had one epileptic whose seizure pattern worsened when Librium was used to manage his hostile behavior.

Many authors mention the drug's hypnotic activity. This appears to result from a reduction in agitation and anxiety with subsequent improvement of insomnia. In many instances bedtime sedatives could be omitted. For moderate insomnia, 20 mg. upon retiring was usually recommended. "Hangover" upon awakening was not recorded. To avoid the daytime drowsiness sometimes experienced by patients at the onset of Librium administration, it might be well to give the largest portion of the daily dose at bedtime.

Side Effects:

In considering the side effects of chlordiazepoxide therapy, time-dosage ratios appear to be of primary importance. The level beyond which significant complications can occur is at the 1 mg./kilo/day or 50 to 75 mg. daily. On lesser amounts, drowsiness or dizziness is occasionally encountered. Some frail, elderly patients become lethargic and unsteady on as little as 25 mg. daily. Tobin and Lewis[7] noted a 20% incidence of drowsiness in psychiatric patients whose dosages are relatively high. Of the 44 cases with this complaint, it was severe in three, and in one was excessive to the point where the medication had to be discontinued. Oth-

ers[4] give a much lower figure; the incidence varying with factors such as dosage, age, degree of agitation, etc. Apparently, this symptom is noted either immediately when high initial amounts are given, or after a few days when the drug accumulates in the system. Of course, in some overactive patients, lethargy can be desirable, but in people who have to function, it is not. The sedative and anxiety-reducing actions of Librium are not necessarily identical and can be dissociated. When undesirable sedation occurs, it is ordinarily due to temporary overdosage.

High dosage complications of Librium administration are reminiscent of cerebellar or cerebello-thalamic toxicity. Ataxia is the most frequently encountered. The incidence varies in different series from 0.3-6.07% with the higher percentages recorded in reports from psychiatrists treating institutionalized psychotic patients. The unsteady, staggering gait is not observed during the first four treatment days. Late in the first week or during the second week, the neuromuscular incoordination gradually develops. Ataxia seems due to a cumulative action of Librium. Associated, but even more infrequent findings consist of leg weakness, dysarthria, adiadokokinesis, vertigo and tinnitus. Secondary complications due to the incoordination may be fractures from falls or car accidents due to impaired reaction time.

Another rare manifestation of Librium toxicity consists of mental confusion, slurred speech, depersonalization and rage reactions. Similar drunkenness has been observed with tranquilizers, sedatives, hypnotics, anesthetics and stimulants. We estimate that increased excitement and hyperactivity occurs in about 5% of high dosage therapy patients. This paradoxical effect is also seen with other tranquilizers; for example, Kline spoke of the "turbulent interval" during rauwolfia treatment. Tobin and Lewis[7] have seen dissociative reactions in 2.4% of their study of 214 psychiatric patients. Typical intoxication states have been reported by Lemere[8] in four of his ambulatory patients getting 80 to 160 mg. for 3 to 10 days. Unfortunately, the cases are inadequately described. It appears that excessive amounts were given without careful control of the dosage.

The remaining accounts of adverse effects are scattered among a variety of organ systems and are infrequent enough to wonder whether a "placebo side effect" may not account for some of them. Constipation, headache, urinary frequency (and retention), decreased (and increased) libido, nausea, menorrhagia and muscle tenderness have been mentioned. Increased appetite and weight gain to the point of being undesirable is mentioned in a few papers. A few erythematous or urticarial rashes in the course of Librium therapy have been seen, but these are rather infrequent.

The first case of agranulocytosis reportedly due to chlordiazepoxide has been published[9] during the past month. It may be well to examine this report carefully, for it exemplifies the "Law of the New Drug"; namely, that complications will ordinarily be attributed to the newest agent the patient has been receiving.

Kaelbling's patient was a 23-year-old female. She received 40 mg. of Librium daily from May 19, 1960 until June 20, 1960. On June 18, sore throat, fever to 102° F., malaise, fatigue and anorexia developed. A tender, enlarged, left submandibular node was palpated. The white blood count was 3,900 with 41% polymorphonuclears. By June 21, the leucocyte count had fallen to 1,600 with no neutrophiles seen on the smear. The red cell count and platelets were within normal limits. Throat and blood cultures showed no growth. Liver function tests were not abnormal and the spleen was not enlarged. A sternal marrow preparation revealed myeloid maturation arrest. Treatment with prednisone, penicillin and folic acid was accompanied by recovery in one week.

The report of this case is ambiguous in two respects. First it states that "from early May, 1960, chlorpromazine in sustained release capsules 150 mg. every 12 hours was prescribed. After 10 days the drug was discontinued since the patient developed mild generalized dermatitis and itching." A skin rash during chlorpromazine therapy had occurred on a previous occasion. Assuming that the chlorpromazine had been started as early as possible in May, namely the first, it would have been discontinued on the tenth. Librium was begun on the 19th of May, nine days later. Yet, later in the article, it is stated "whether the brief course of chlorpromazine hydrochloride which had been terminated *one month* previously facilitated the onset of this complication (agranulocytosis) cannot be answered." As a matter of fact, a dermatitis preceeding the onset of phenothiazine agranulocytosis is not uncommon in our experience. Either chlorpromazine or chlordiazepoxide could have caused the agranulocytosis, but the former drug is proven to be capable of producing agranulocytosis.

It is Kaelbling's belief that periodic white and differential counts are helpful in detecting the earliest stages of agranulocytosis. This was not so in the present instance, for on June 18, 1960 a leukopenia had existed, yet the patient received the drug for two additional days. It would seem quite unnecessary to perform routine, periodic laboratory studies on patients receiving chlordiazepoxide on the basis of the cited study.

There is no report of addiction to Librium in the literature although a case report along these lines is inevitable. This is said not because I think that it is an addicting agent, but because there are people whose personality configuration is such that they will fasten upon any drug of this sort. In addition, we have had a few patients who preferred Librium to all other tranquilizers because of the mild euphoria that they experienced. Ordinarily, this is a desirable action, but one which could lead to its habitual use. Withdrawal symptoms are not mentioned in the literature even when large amounts are suddenly stopped. However, the manufacturer's brochure mentions that convulsions might accompany abrupt withdrawal. As mentioned, cumulative effects may develop over a period of days or weeks so that dosage readjustment is more important with Librium than with a drug like meprobamate. Even after the optimal maintenance dose has been found, occasional patients may become tolerant over a period of months and an increase of dosage may be necessary.

During the month of October, 1960 and subsequently, a brisk correspondence appeared in *The Lancet* concerning chlordiazepoxide. The "Letters to the Editor" columns of the English medical journals appear much more diverting and animated than ours. In this instance a note by Ingram and Timbury[10] started the exchange. They mentioned that in fifteen anxious or obsessive patients treated with chlordiazepoxide, side effects were high and the improvement rate low. Their dosage schedule was 10 mg. t.i.d. the first week, then 25 mg. t.i.d. for the second and third weeks. Five of their patients became drowsy, two fatigued, apathetic and dizzy, two were irritable, and one schoolmaster struck his wife for the first time in twenty years. Three of these patients had to stop work and two refused to continue the medication.

In the rash of letters that followed, the consensus was that Librium was not a dangerous substance and that it did give symptomatic relief. The nature and incidence of adverse reactions were relatively low and never serious.

A review of Librium's side effects reveals that somnolence and perhaps dizziness may be experienced in the low dosage range. Patients getting more than 1 mg./kilo/day for more than a short period should be observed for the development of symptoms of cortical and cerebellar in-

toxication not dissimilar to that seen with alcohol. An unsteady gait or impairment of skilled movements should serve as a warning that reduction of dosage or temporary elimination of chlordiazepoxide is necessary.

The agent under consideration has a substantial margin of safety between therapeutic and toxic effect when it is used properly. In an effort to obtain further human safety data, a particular search was made for cases of attempted suicide with Librium. Since it was being prescribed for depressed, agitated and psychotic patients, it was expected that a few patients might utilize the medication for purposes of self-destruction. Five such instances were collected to date, and summarized. (Table I.)

Librium may be a worthwhile medicament to prescribe when the suspicion exists that the distraught patient may use the medication as a suicidal agent.

Dosage and Administration:

For medical-surgical, ambulatory patients, small initial amounts, for example, 10 mg. one to three times daily would be prudent. These are people who have to drive and work efficiently, and any untoward effects should be avoided. In fact, these people tend to discontinue medication if it makes them sluggish or drowsy. After a few days, the dosage can be increased or decreased. In general, the greater the tension state the higher the dose required, but this is by no means invariable. If the anxiety has been satisfactorily contained, thought should always be given to further decreases in the dose, or to stopping the drug. Anxiety in the nonpsychiatric patient is ordinarily not fixed, and elimination of its physiologic and psychologic symptoms may give the patient the opportunity to reestablish his prior emotional level of functioning.

In the acute delirium states, as in delirium tremens, large quantities are given and these may be via intravenous route. Ticktin and Schultz[11] recommended 50 to 200 mg. intravenously in a 1% solution depending on the severity of the patient's disturbance. One hundred mg. is their median dose, and this can be repeated in an hour or two if necessary. The onset of action was either immediate or delayed for 15 minutes. A single dose was effective for about three hours. After oral administration quieting effects may be noted about a half hour after the first dose and the activity is rather prolonged. Probably, Librium can be effectively given only twice a day during the maintenance period.

Chlordiazepoxide has been prescribed with other psychochemicals without in-

TABLE I

Suicide Attempts with Librium

Author	Patient's Age	Sex	Amount Ingested	Period of Ingestion	Treatment	Symptoms	Outcome
1. Clark, T. P.	22	M	1630 mg.	24 hours	Coffee	Drowsiness Ataxia Dysarthria	Recovered
2. Clark, T. P.	—	—	875 mg.	Single dose	Coffee	Drowsiness Ataxia	Recovered
3. Kinross-Wright, J., et al.	30	F	625 mg.	Single dose	Gastric lavage	Comfortable night's sleep	Recovered
4. Hines, L. R.	47	F	1150 mg.	Single dose	None	None Mentioned	Recovered
5. Hines, L. R.	22	M	1600 mg.	24 hours	No lavage	None mentioned. The patient required calming	Recovered

compatibility. The amphetamines, imipramine and the phenothiazines have all been used concomitantly. Electroshock treatments are not incompatible with Librium therapy. The combination of chlordiazepoxide and the amine oxidase inhibitors is probably safe, we have never encountered difficulty with this combination. Pipradol (Meratran) has been used in combination with Librium when drowsiness was excessive with the latter drug.

Results

Some of the results of treatment with Librium have been mentioned when the indications and side effects were considered. It seems generally agreed that the drug is effective in the majority of tension and anxiety states. Since it does not ordinarily interfere with mental alertness or curtail motor performance in the amounts required for the office patient, most clinicians find it a worthwhile compound.

Unfortunately, there is a dearth of controlled Librium studies for the anxiety and depressive reactions. It is hoped that these are under way. The information regarding Librium's activity as an anticonvulsant and muscle relaxant is insufficient to make a definite statement about efficacy.

It is unnecessary to cite the long list of medical and surgical conditions in which Librium has been used, and in which improvement has been reported. These may all be subsumed under the concept, previously mentioned, of altering the affectual response to physical illness, or of decreasing anxiety and its physiological discharge. Whether the autonomic manifestations of anxiety cause the syndrome as in hyperventilation, or whether the anxiety is a result of an established disease as in the patient aware that he has a malignancy, it seems immaterial. Librium has favorably influenced the anxiety of both types in a majority of our cases.

Summary

Librium is a relatively new drug and until now its evaluation has been based essentially upon clinical reports. Nevertheless, it has been so widely used, and the reports are consistent enough to conclude that it is quite effective in the control of disabling anxiety. Anxiety is a core effect which can influence the course of any disease process. Its amelioration is sometimes necessary and often desirable in medical practice.

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GENERAL DISCUSSION

MORNING SESSION

Q. *Dr. Griffith Barlow:* If urinary excretion of Librium is slow, and blood levels high up to 96 hours, why divide the doses over the day?

Dr. Sidney Cohen: This merely tells us that Librium has a cumulative action. In our experience, Librium does not have to be given more than twice a day.

Dr. Randall: Our studies on blood levels in humans are still limited, so that we cannot be positive about these cumulative effects as yet. We do know that a single dose has a half-life of two days, based on a patient who was studied with radioactive drug; when the dose was 150 mg. a day for two days, there was a build-up. However, the study was done in the early days before it was realized that Librium was such a potent drug and this enormous dose was used; with time the doses were gradually reduced to 10 mg. three times a day.

There is no doubt that large doses, i.e. 50 mg. t.i.d., build up high blood levels which because of slow excretion stay high for a long time. But with therapeutic doses of 10 mg. t.i.d. there is only a slow build-up to the therapeutic level. Then equilibrium is reached as the body eliminates the drug at about the same rate as it is ingested, and a single dose might last several days. Daily doses of 30 mg. usually do not accumulate to an abnormal amount, equilibrium being reached between the dose taken and the amount excreted, destroyed by the liver, or by some other still unknown mechanism. Much about the metabolism of this drug is still unknown, because the many breakdown products make this a very difficult problem. The same is true of compounds like Marsilid or Marplan, both drugs having a long duration of action; yet, doctors prescribe these three times a day. But we do not know the rationale for this.

Q. *Dr. Barlow:* Is there a variation in gastrointestinal absorption? Have there been supportive blood studies?

Dr. Randall: The difficulty with blood level studies is that the methods are too insensitive to pick up the effect of 10 mg. doses. With doses of 50 mg., we can measure the blood levels by the Bratton-Marshall technic, a method used to measure the sulfonamides which are given in grams/day. Except with very large doses which lead to high blood levels that we can measure, correlation of clinical activity with the dose, or even ataxic effects, is not yet possible.

Q. *Dr. Ditman:* With the phenothiazines the excretion rate is proportional to the fluid intake. Does this hold true for Librium?

Dr. Randall: I doubt it. I think that the compound is metabolized, probably, by the liver, and the rate of the metabolism is somehow regulated by the intake. We know that, with many drugs, the rate of metabolism is controlled by the amount taken in, and as the liver gets used to metabolizing a drug after several days, it gets rid of the compound as it is taken. In my opinion the liver can take care of this drug preventing accumulation of dangerous amounts. This is the reason why the dose has to be adjusted to the patient's needs and the ability of the liver to take care of it.

Q. *Dr. Thomas MacVeach:* Dr. Norman Cohen, your nine-year old patient, awaking in terror, makes me think of another attack which occurs in sleep, sleep paralysis. Is this related to epilepsy, and, if so, would you recommend Librium?

Dr. N. Cohen: Sleep paralysis is usually grouped or categorized with the syndromes called "narcolepsy." Narcolepsy, probably related to epilepsy, perhaps involves the hypothalamus; sleep paralysis is frequently part of the syndrome.

In sleep paralysis the individual wakes up in the morning without the writhing and twisting movements seen in our patient, and without terror; on the contrary he finds that he cannot move until he is touched by someone else. The patient usually lies perfectly still, but awake; only after he is touched, is he able to get up and move about normally.

As for treatment, I know of nothing that helps sleep paralysis. Librium probably would have no effect, but, certainly, it could not harm.

Q. *Dr. Rathbone:* What is the method of withdrawal from Librium and the expected effects? I have tried to take patients off and find that they do not do well. I found it tremendously enhanced by the addition of Tofranil. I had thirty cases—each with agitative depressions, involutive melancholias, and some with ventricular ectopic beats. Numerous drugs—sedatives, quinidine, potassium bromide—were tried with no effect. Librium worked well when I added Tofranil, but it did not do it alone. I wonder what the chemical association could be?

Dr. Sidney Cohen: I don't know whether the effect of the Librium-Tofranil combination is greater than might be expected from each

alone. I would say in answer to your first question that it would be prudent to de-crescendo the dose of the drug, if possible. What you may be seeing is a release phenomenon. You were controlling the agitation with Librium and Tofranil and then, upon decreasing it, especially abruptly, these people lost their control which triggered a resurgence of their prior symptomatology.

Dr. Rathbone: All of these patients that I have, have had at least two years of shock treatment, many of them eight to fifteen treatments a month.

When I used Librium originally, I had fair results. The patients seemed to do well; then they had to come back because of ventricular ectopic beats and periods of anxiety. With the schizophrenics, there was almost no benefit with Librium alone.

But Librium with Tofranil, in my experience, has produced 100 per cent benefit. I don't know why. I have tried countless other drugs, and none of them worked. As I said, I had about thirty people who are entirely well and useful.

Q. *Dr. Doyle:* What about the use of Librium in hyperkinetic school children?

Dr. Sidney Cohen: My practice at the Veterans Administration includes very few hyperkinetic school children. The reports in the literature are anecdotal, but good results in small series are noted.

Dr. Nicholas Bercel: I had experience only with nine, each of whom had some EEG abnormality, but no seizure discharge; as I stated, six responded well, two did not, and one became worse. However, in this group we used placebos, and I do not remember how many did just as well, or just as poorly on the placebo as on Librium. The case material, however, was highly selective because only those that had EEG abnormality were taken, and there is at least some suspicion that these are not the garden variety of hyperkinetic, emotionally disturbed children whose condition is psychogenic. With that type of children, I have no experience.

Q. *Dr. J. F. Shalwick:* Is there any report of aplastic anemia with Librium?

Dr. Sidney Cohen: No.

Q. *Dr. Harry Fisk:* How do you account for the appetite-stimulating effect of Librium? Why is it of no value in the nervous, compulsive eater?

Dr. Randall: Our observations were that starved animals took in more food in a 4-hour period than the normal animal under the same conditions. If we feed the animals chronically with the drug, there is an increased weight and an increased food intake over a period of thirty days, three months or more. We have no explanation for this at all.

We have our own evidence and evidence from outside investigators, that there is also an increased water intake. Something happens in the animal so that he wants more food and water over a short period of time, and increases its food intake over a long period.

I am not familiar with the clinical reports except to say that, occasionally, increased food intake in humans has been observed. I have no idea what the mechanism is. . . .

Dr. William G. Clark: Other than the known fact that lesions particularly the hippocampus, can increase hunger and thirst to the point of causing enormous obesity in some animals. This has been described for goats: the animal takes in literally gallons of water, and quintuples its weight. This is another indication of the area of action of this drug.

Q. *Dr. Bercel:* In the second half of this question—"Why is it of no value in nervous, compulsive eaters?—my experience is that it actually improves appetite in humans in this group so that they eat more.

Dr. Ditman: I think Dr. Mooney has some figures on eating.

Dr. Horace B. Mooney: The patients we treated were alcoholics, who after four weeks showed a tendency to gain more weight than those who received the placebo.

Q. *Dr. Ditman:* Has Librium been used in children to prevent febrile seizures, children with normal EEG's who have convulsions with temperatures of over 103°?

Dr. Bercel: I have used it in a few instances, but as a rule in febrile seizures, with normal EEG's which, of course, you may not know at the time of the seizures, it is better to rely on well-established, highly effective anticonvulsants (Dilantin and phenobarbital), particularly for the grand mal seizures. I would not use Librium or any drug other than these two as my first choice.

Q. *Dr. Jacobson:* Do you think routine blood counts are of any value in out-patients taking Librium or phenothiazines when the patients are instructed to report all symptoms?

Dr. Sidney Cohen: I would like to emphasize that I do not think they are of any value. This is more pertinent to the phenothiazines than to the group under study today. The three cases of phenothiazine agranulocytosis that I have encountered were all diagnosed clinically despite the routine biweekly white counts and differentials which the patients had been getting. With Librium, the rationale for periodic blood counts is even more obscure. It would be more profitable to spend

the money and time involved in laboratory work in clinical observation of the patients on phenothiazines. They should be told to report sore throats, fever, rashes or swollen neck glands immediately. The physician should take these symptoms seriously, withholding the drug until the blood count has been determined.

Q. *Dr. Talbot:* What was the per diem dosage of Librium given to epileptics excited by Librium medication?

Dr. Sidney Cohen: In psychiatric patients the usual dose was about 75 mg./day.

I will take a moment to answer a question. Doctor Clark has sent in this note: "Aren't you going to describe Doctor Nagy's case?"

Dr. Nagy of Sepulveda had an instance where a manic episode occurred during the treatment with Librium in a psychiatric patient. He was in remission on maintenance Thorazine, and an attempt was made to substitute Librium. He developed an excited, violent episode. The literature contains instances of paradoxical increases in anxiety and destructiveness during Librium treatment. The figure is well below 5% of high dosage cases.

Q. *Dr. Ditman:* Was the removal from Thorazine ruled out as the cause of excitement?

Dr. Clark: I don't know.

Dr. Mooney: It seems to me that to prove a paradoxical effect you would have to repeat it. It could very well be due to an exacerbation of the illness itself.

Q. *Dr. Ditman:* How soon after a single oral dose is there a tranquilizing effect, and how long does it last? What is the best dosage schedule?

Dr. Randall: In animals onset is quite rapid with this compound. With the epilepsy test, for instance the Metrazol test, we can certainly demonstrate it within half-an-hour by the oral route in mice. Mice have a quite rapid metabolism; they take it in fast and get rid of it fast, and so the duration of action is about six or eight hours. In the rat as seen in the avoidance test, activity is shown within half-an-hour, and duration of action is again six to eight hours.

The effects of large oral doses in a monkey can be seen also within half-an-hour, and these effects last for as long as two days. The major effect is over within 24 hours, the taming effect is mostly gone by 24 hours, but, with a second dose after 24 hours, you see an added effect over the first indicating that there are residues of the drug still around. Duration of action certainly depends on the animal species, but I cannot answer about the dosage in humans.

Dr. Sidney Cohen: I think we have all observed a rather rapid onset of action with oral Librium—within an hour; with intravenous administration, it is within 15 minutes.

Q. *Dr. Ditman:* Dr. Cohen, is there any preferred treatment for overdosage? You seemed to imply that coffee was of value.

Dr. Sidney Cohen: Induced vomiting or gastric lavage is recommended. A cathartic should be given; coffee, if the patient can swallow; otherwise use one of the amphetamines.

Dr. Theodore Rothman: With respect to Tofranil and Librium in pseudoneurotic schizophrenics, those who have gotten help have been on a combination of both drugs. However, this may be only a chance observation for which there is no explanation unless a controlled study is done. I think this is one of the most important things that must be done for a true evaluation of the drug.

Q. *Dr. Mary Fletcher:* Have there been any reports on the use of Librium in normal children or adults? We have noted behavior disturbances in the normal child on 2 mg./kg.

Dr. Sidney Cohen: I suppose you are referring to the normal, unruly child, or the normal, urban, tense adult who has difficulty unwinding and sleeping.

Dr. Ditman: Two mg./kg. is a fairly high dose.

Dr. Fletcher: I will explain what I meant by the "normal" child. We have been giving Librium to 134 children with strabismus, that I refer to as otherwise normal children. Librium in doses of 2 mg. per kilo has been demonstrated to be a muscle relaxant in children with esotropia. My question related to the high percentage of behavior disturbances we noted in these children.

Q. *Dr. Sidney Cohen:* Would you please clarify two things: 1) was the strabismus corrected with Librium, 2) were the behavioral disorders caused by the medication, or did they improve with Librium?

Dr. Fletcher: We could demonstrate improvement in strabismus, that is, in a child's eye that was crossed inward. We could actually measure uncrossing of that eye, which is what I mean by improvement.

In these children, we noted all of the side effects that have been described here, but in addition, a significant percentage of the previously normal children with no behavioral problems became incorrigible in behavior and began to fail in school. These important reactions in an otherwise normal child occurred on 2 mg./kg., but not on lower dosages.

Dr. Sidney Cohen: Theoretically, I can postulate a mechanism whereby a normal child

could become unruly, as you describe. These children are getting high doses, and their ability to control themselves, their spatial perception, are all disturbed at that dosage level. I would think that the ego mechanisms by which they remain good, obedient children is likewise disturbed, and they lose control, just as if they were fed perhaps three Martinis a day.

Dr. Oettinger: Most of our electroencephalographic data on children with strabismus, show a high incidence of reciprocal temporal abnormality in 50 to 70 per cent of those who are otherwise normal. I would make the same comment as Dr. Cohen about the high dosage, and in relation to coordination defects and disturbing behavior.

Dr. Joseph C. Elia: In many of our patients with cardiospasm, I have noticed the same thing that Dr. Fletcher talks about. The emotional problems with a great number of these, eventually lead to an organic change. The muscle relaxant drugs have been the only thing we have had so far for cardiospasm.

Since we have been using Librium as premedication to inhibit the gag reflex in laryngoscopy and esophagoscopy, it has become much less of a problem, because obviously, the emotional component involved has been eliminated or reduced.

Q. *Dr. Ditman:* What dosage do you use in anesthesia?

Dr. Elia: Thirty milligrams, about two hours pre-operatively as well as the same dose the night before. Prior to a tonsillectomy, we tend to use a somewhat higher dose.

Q. *Dr. Rothman:* When I was in Dr. Randall's laboratory, I believe he demonstrated the bimodal action of Librium: as a stimulant and an antidepressant. These two different types of effects can be seen in the patient under clinical study. Some become dis-inhibited, while others become much calmer, but the drug may have a definite stimulating effect at first when the patient is unpredictable. Is there something in the pharmacological work that would show this?

Dr. Randall: The characteristic response in animals is one of sedation, quieting; I do not recall the experiment in which you say we showed stimulation.

Q. *Dr. Ditman:* By stimulation, do you mean impulse-ridden?

Dr. Rothman: That is right.

Q. *Dr. Ditman:* Did you see anything that is comparable to impulse-ridden humans, in animals where they become aggressive?

Dr. Randall: Not in my experience.

Q. *Dr. Ditman:* Is it the blood level or tissue level that is important?

Dr. Randall: Again, when we are using only large doses, we find that the material goes into all the tissues, and of course the more in the blood the more in the tissues. We find more in the liver, and in the kidney, and the fat has quite a bit.

The material certainly is in the tissues and comes into equilibrium with the blood fairly rapidly—within a half-hour. It stays in the tissues for some time, gradually going back into the blood stream, and is then inactivated, probably by the liver, or slowly excreted by the kidney. Certainly, the tissues, as is true for many types of drugs, act as a storage depot.

Q. *Dr. Molle:* Are there any contraindications to the use of Librium, such as hepatic disease, and have any studies been done with psychotic patients?

Dr. Sidney Cohen: There appears to be no contraindication to the use of Librium in liver disease. I would think as with any drug excreted in the urine, that, if there is incomplete clearance of metabolic waste products by the kidneys Librium would also be included.

Q. *Dr. Robert Pogran:* Considering the stress that is expected to be imposed upon man in a space-vehicle system, namely, sensory deprivation, zero-gravity environment, vertigo, and disorientation, etc., and keeping in mind that the human judgment and decision-making capacity must be optimal, do you feel that Librium has some practical application in this regard?

Dr. Sidney Cohen: The question of chemical regulation of the astronaut is a proper concern of psychopharmacologists. Librium would have no role as an alerting drug. If a hibernating agent is required the phenothiazines seem more appropriate than the benzodiazepines. I have put too few people into orbit to offer you reliable data.

Q. *Dr. William Clark:* Has it been studied in conjunction with psychotomimetics?

Dr. Sidney Cohen: There are no reports on the abolition of psychotomimetic effects to date with this particular drug.

Q. *Dr. Abraham Friend:* Would Librium be better than phenobarbital in combination with Dilantin in the control of severe epileptic seizures?

Dr. Bercel: It all depends upon the form of seizure: in grand mal seizures, Dilantin or any other hydantoin with a minimal amount of barbiturate added might be best.

In psychomotor seizures, I would definitely prefer Librium over phenobarbital as the addition to Dilantin, but, as I have indicated in my paper, Dilantin was not the best drug for the combination. Mysoline and Librium were the best in combination.

Q. *Dr. Ditman:* The impression I got from Dr. Randall's chart, was that the broadest spectrum of seizure control was a combination of Librium with phenobarbital in the three tests that he used in seizure activity.

Dr. Bercel: In animals that was the case.

In clinical studies this would not be a good combination for petit mal alone. Phenobarbital and Librium would go together in a petit mal-grand mal syndrome. The combination would serve in psychomotor grand mal, but I would not substitute it for every type of seizure, for instance, petit mal alone, or grand mal alone. You would have to give a great deal of Librium in order to get the anti-convulsant protection that you get from Dilantin or Dilantin and phenobarbital.

Q. *Dr. William G. Clark:* I would like to hear some comment on potentiation of analgesics with Librium clinically.

Dr. Sidney Cohen: This is an unclear area to me. There are comments that it does not do so. This, of course, is important when we are dealing with the treatment of the tense alcoholic, for example. We should try to form an opinion about whether Librium plus alcohol is a dangerous combination, but on this there is confusion in the literature, and we will have to wait for a final word on it.

Q. *Dr. Barlow:* What is the effect on grief, independent of anxiety? Is there any application in acute coronary thrombosis?

Dr. Sidney Cohen: It is indicated in patients with coronary thrombosis if they are suffering from marked anxiety, just as are phenobarbital and meprobamate for the same purpose. I prefer to think of grief as either non-pathological or pathological. Mourning is a very important human expression of object loss which must be released. If it is suppressed it may result in chronic depressed states. I would not treat object-bound grief with Librium. However, in protracted, pathological grief which goes on and on, without diminution long after grief in which the psychic loss has long since passed, psychotherapeutic intervention becomes necessary. In such instances drugs like Librium may be worthwhile adjuncts. I wonder what Dr. Hayman thinks about this.

Dr. Max Hayman: Librium has been used in patients with agitated depressions; here the symptoms are both of anxiety and depression, and many patients have recovered from both manifestations. However, one patient said that his anxiety was relieved but his depression was deepened. As a matter of fact, he discontinued the therapy on this account. So, apparently, they do not work together in all cases.

Librium on Athetoid Paraplegics (Film)

ROBERT F. LIVINGSTON, M.D.*

Dr. Keith S. Ditman: The next presentation is a film entitled "Librium in Athetoid Quadriplegia" presented by Dr. Robert F. Livingston.

Dr. Robert F. Livingston: The film that we saw this morning on the use of Librium in wild animals actually suggested taking the film on this first patient. You will see that he is a very hyperactive, twenty-pound five-year old boy.

At the time this film was made, the child was receiving phenobarbital, grains I, t.i.d., Compazine, 4 mg. every six hours, and reserpine, 0.25 mg. every six hours. As you will see, this regimen was not very effective. This patient was the fourth child after a two-hour labor, and, for 45 minutes after birth, had artificial respiration. Soon after, convulsive seizures began, and his whole course was one of slow physical development, idiot-level of intelligence, and continuous active athetoid movements in spite of heavy sedations.

When he was admitted to Sonoma State Hospital, November 18, 1958, he was nearly four years of age, very small—31½ inches, 17 lbs. 2 ozs.

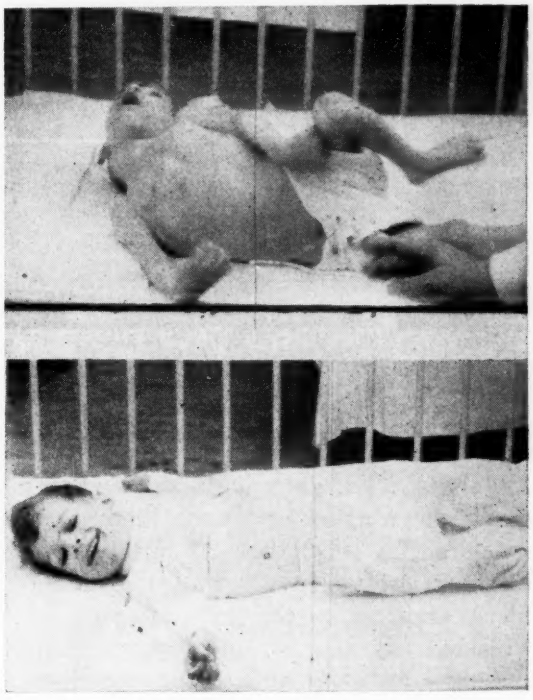
He was having very active, writhing movements in spite of the phenobarbital, grain I, three times a day on admission. As mentioned, Compazine and reserpine were added. He is a rather good-looking boy who smiles, recognizes his mother and the people that take care of him. He can grasp an object; he has no other developmental activity. He cannot support his head, turn or sit. No other abnormalities were found on physical examination other than his very slight weight and very active movements.

Needless to say, feeding and nursing care were very difficult.

March 8, 1960, Librium, 10 mg. every three hours was begun with remarkable and prompt improvement. Within 24 hours all the other medication was discontinued. The child was maintained on 25 mg. t.i.d. He developed a little increased athetosis, and, on October 7th, this dosage was increased to 35 mg., t.i.d., on which he has been maintained to date. He has gained 4 pounds; blood studies have remained normal. He has had no discernible complications, and, as you will see in the follow-up film, is much more manageable.

We were quite at a loss about what to do with this boy. He had two bouts of pneumonia with this kind of activity. He ate well but, literally, was destructively hyperactive, and, in spite of padding the crib, he would bruise himself. I think you will see that he is quite a different boy.

Dr. Keith S. Ditman: Were his movements present during sleep?



Case 1: Before and after treatment.

*Sonoma State Hospital, Eldridge, California.

Dr. F. Livington: No, they were not.

Question from the Floor: Any improvement in his mental condition?

Dr. Livingston: Actually, his intelligence is so low that I do not think we can detect that. Outside of recognition, a smile, and a grasp, he has no other activity. He is now over five years of age.

Question from the Floor: Could he grasp any objects now?

Dr. Livingston: He does not make any use of them, but he will grasp an object if you put it in his palm.

Dr. Ditman: He seems very flaccid.

Dr. Livingston: There is no element of spasticity in this lad, but I don't know whether I would call it "flaccid."

Dr. Ditman: Could he roll himself over?

Dr. Livingston: No, he does not. He has never turned.

Question from the Floor: How long has he been on the medication?

Dr. Livingston: This was begun in March, 1960. He has been on the 35 mg. dosage since last October. He was maintained on 25 mg., t.i.d., at first, and there seemed to be a gradual increase in athetosis.

Question from the Floor: What is the date of these films?

Dr. Livingston: These films were made in November, 1960.

Question from the Floor: How was the medication administered?

Dr. Livingston: Orally, in 25 mg. capsules, and now we have added 10 to that. He eats well. Taking things orally is not one of his problems.

Question from the Floor: Why did you increase the amount of Librium?

Dr. Livingston: Because of his increased activity. He was dangling his arms and legs in the crib again and bruising himself; he became quite hyperactive, significantly so, but nothing like he had been originally.

Question from the Floor: Any abnormal EEG?

Dr. Livingston: No, an electroencephalogram on March 5, 1959 was interpreted as a normal, Thorazine-sedated sleep record.

This second patient is a 20-year-old man. Born after a 12-hour labor, he did not breathe for 20 or 30 minutes after birth. Cerebral palsy was diagnosed at birth, and his development was very slow. This lad was considered of average intelligence, and he was afforded considerable advantage in schools and clinics, but had progressive deterioration, and came to our hospital on May 5, 1950; gradually, his athetoid movements reduced him to a bed patient, a difficult nursing problem.

Over a period of months, from April to August, 1958, a series of neurosurgical thermal lesions were produced in the thalamus and globus pallidus at a San Francisco Hospital, without relief of his athetosis.

As you see, he is very thin. At the time this medication was begun, he weighed 65 pounds. He thrashed continuously in his crib and it had to be padded. He also was unable to turn over, sit, or speak.

June 28th, 1960, Librium, 10 mg. was instituted. My only other experience having been the first patient, I started this boy also on 10 mg. every three hours. The following day he was much improved, but the day following that, after a total of 19 doses, he was unable to swallow. We stopped medication, of course, and within eight hours he was taking foods and fluids again, but for 13 days his athetosis was removed.

When it returned to approximately the previous level, we started him on Librium, 5 mg. three times a day, and he has been maintained on that ever since, making his care much easier.

The third patient is a 26-year-old man. He was the fifth child of the mother in a 3-hour labor. We do not have any details about his birth history. However, convulsions occurred at four days of age, and he never sat, walked or talked.

He was admitted to our hospital at four years of age, and at that time his weight was 30 lbs. 11 ozs., and his height 39 inches. He, also, had idiot-level intelligence.

At the time this treatment was begun, he was a 76 lb., 26-year old, with continuous writhing athetoid movements. His treatment was begun on October 26, 1960. Five milligrams Librium, three times a day, was started, and the movements were promptly reduced within 24 hours. Simi-

lar to the first child, he had an increase of athetoid movements after a period of time.

On December 21, in other words, after approximately two months, he is on 5 mg. four times a day, on which he was begun, and has been maintained since.

As you will see in a moment, it was possible to get this boy up in a wheelchair, which was quite a change.

Question from the Floor: With this impairment in his condition, was there any improvement in his mental status?

Dr. Livingston: In each case, the level of intelligence, I think, was so low that this would be difficult to measure.

Question from the Floor: I would like to know, Doctor Livingston, if you have heard of any experience in the treatment of Huntington's chorea with this.

Dr. Livingston: No. I think this would be interesting, but I have not.

Question from the Floor: In the second case, you suggested that the patient had difficulty in swallowing.

Dr. Livingston: It is not so much a difficulty in swallowing; it is just mechanically difficult to feed him. He moves around constantly, flails his arms, and it is pretty much a game of "catch" for the technician to feed him.

Question from the Floor: This was not a Parkinson-type of reaction?

Dr. Livingston: No, I think not.

Dr. Ditman: Dr. Hines, did you have a comment?

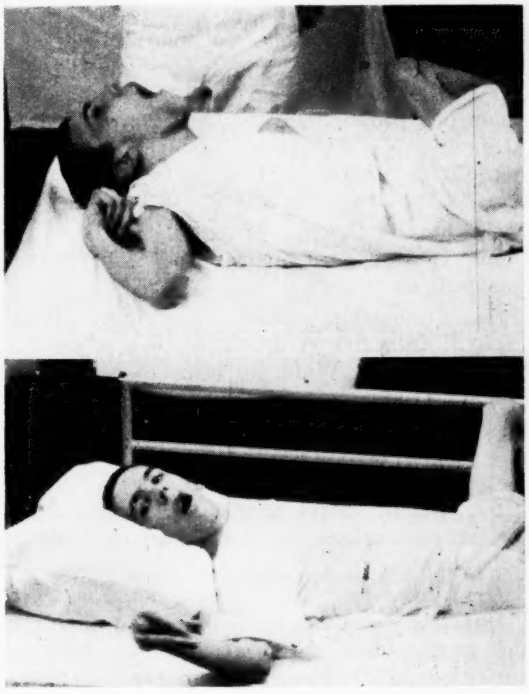
Dr. Hines: In connection with the question regarding Huntington's chorea, I have no other details, but there is a man in St. Louis who is doing some work on this. I could get the details for you. I know it was reported favorably in a letter.

Question from the Floor: First, were these patients ever tried on amphetamine, and, secondly, was withdrawal of the drug ever tried to see what would happen?

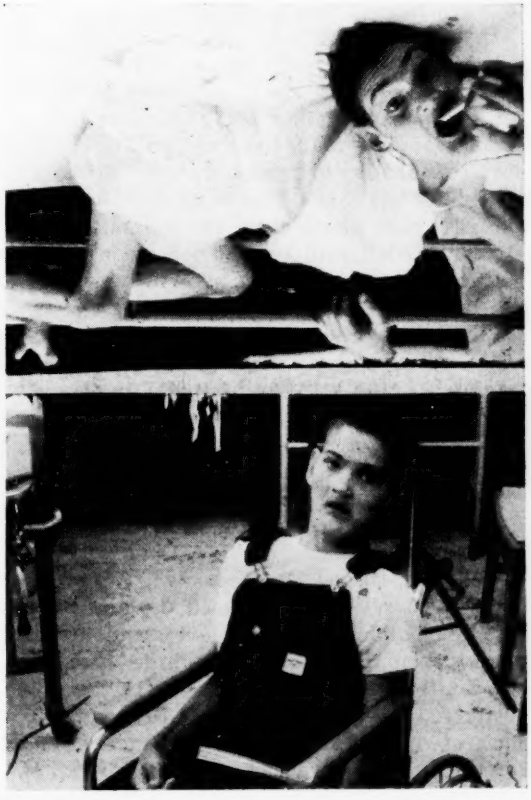
Dr. Livingston: The answer to both questions is "no."

Dr. Ditman: I wonder, Doctor Livingston, if you might be able to explain the difference in the amount of dosage you give. With smaller individuals, you use a higher dosage than in a larger individual.

Dr. Livingston: The only way I can explain this is the greater hyperactivity. The first patient was the first one we tried, and, as I mentioned, we began to treat the 20-year-old



Case 2: Before and after treatment.



Case 3: Before and after treatment.

man with the same amount, and, to my amazement, he had this complete ablation of activity. Of course this is an insignificant experience, but it would seem that the dosage was somewhat proportional to their hyperactivity. Also, in two of the cases, there seemed to develop some tolerance; that is to say, after a time on the drug, the activity increased again.

Dr. Sidney Cohen: Were any of these patients treated previously with other muscle relaxants or tranquilizers?

Dr. Livingston: Yes. The baby—I say "baby," he is five years old—had a whole battery of things. When he came to us, we had him on Compazine, reserpine, phenobarbital; perhaps in adequate doses, it is a relaxant. He was on 1 grain, t.i.d., at that size, and acting like you saw in the film.

Dr. Cohen: More particularly, what about the muscle relaxants, meprobamate, Flexin, Robaxin?

Dr. Livingston: No, we have not used these.

Question from the Floor: Do you or any of the group have any experience in treating non-athetoid, hyperactive, mentally-retarded with Librium?

Dr. Livingston: We have some of these patients. We have not had any organized study to learn more along these lines.

Dr. Rothman: What made you use Librium? What was the thought behind it?

Dr. Livingston: As I mentioned at the outset, we had used other things, and had considerable trouble with the first child. I asked our consulting neurologist, Dr. William J. Wedell, to see him. The same day Doctor Wedell saw him, along came the animal film, and Doctor Wedell said he did not have anything better to suggest. That is how we came to use Librium.

Dr. Rothman: Just empirically?

Dr. Livingston: You might say "stumbled" into it. Actually, that is how I happened to make the film.

Dr. Rothman: You were also surprised, I think.

Dr. Livingston: That's right.

Dr. Rothman: And you were interested in the spasm.

Dr. Livingston: Well, he was actually destructive. We had increased dosages of barbiturates almost to sleep level, and upon reducing them, he would bruise himself. He had two bouts of pneumonia along with the hyperactivity. So, he was quite a problem. This suggested taking a film of him, and accounts for the fact that we have a record of it. It is a very limited experience, but I think a rather interesting one.

Dr. Harry Grayson: Was the drug tried in any other children?

Dr. Livingston: We do not have any others of this degree of activity. A number of the staff have tried it on athetoids with largely satisfactory results, but these are the most hyperactive we have had.

Dr. Ditman: The question by Doctor Sidney Cohen is: "Is there any experience with Librium, drug-induced or other Parkinsonism?" Doctor Bercel—

Dr. Nicholas Bercel: I have tried to give it to those who did develop the drug-induced parkinsonism symptoms, and it does not work. There is no use trying when Cogentin and various other anti-parkinsonian agents are so effective. On the other hand, I have never seen any parkinsonism symptoms develop by the prolonged use of Librium even in large doses.

Dr. Thomas McVeach: Is Librium useful in Parkinson's?

Dr. Bercel: I have only used it in one patient, a physician, as a matter of fact, who was exceedingly restless in the evening, and was confused and tried to run away, after he had one of these operations in San Francisco. I was afraid to use other injectable phenothiazines because, as you know, they have definitely parkinsonian liability. I have used 50 mg. of Librium, intravenously, two or three times, one day each, and it quieted down; we never had to use it since about a month ago. That is the only experience I have had with it in Parkinson's. It is well tolerated.

Dr. Podrom: I would be interested to know whether there were any hematological factors in these patients you examined, Dr. Livingston. If you have done this, that might be a common denominator if there is any alteration as the result of Librium.

Dr. Livingston: I do not know if you have anything more specific in mind, but routine counts have not shown any changes. I was interested in the comment this morning that perhaps these are not too reassuring if done periodically; but do you have any other studies in mind?

Dr. Podrom: I was thinking of oxygenation in this blood therapy—any factors that result from hypoxia. It seems that there might be seizures, some degree of respiratory paralysis, or spastic type of respiratory movements.

Dr. Livingston: I have had no experience with that. I wish the Panel could comment on this.

Dr. Ditman: Dr. Randall, does Librium make any changes in the degree of oxygenation of blood due to, perhaps, changes in respiration?

Dr. Lowell O. Randall: Certainly not in our animal experiments. We have done quite a number of experiments with this drug for over a year in rats without any change in blood counts, at least six months in dogs followed with blood counts at intervals, and certainly no change has occurred on quite high doses, doses that sedate the dog, and, still there is no change in blood counts.

As to oxygenation, I do not know. There is no effect on respiration directly, even up to very high doses. No acute effect.

Dr. Ditman: I got the impression from the films that there was some impairment of respiration prior to medication. In other words, that the athetoid movements were limiting respiration. Is that correct?

Dr. Livingston: No, I don't think so. Of course, as active as that first patient was, you would almost expect him to be breathing rapidly, but I believe he was never in any particular respiratory distress.

Dr. Bercel: You can add number six to the five cases that tried Librium with suicidal intent. My patient thought it was a new sleeping pill and swallowed, in one slug, 1,000 mg. of Librium. This patient had no respiratory depression, slept about 12 hours, had a hangover for another 12 hours, and came out of it without any stimulants.

Dr. Cohen: Any treatment?

Dr. Bercel: No.

Dr. Cohen: How old and what was the sex?

Dr. Bercel: Female, 26 years old. I stood by, but I did not use any treatment. I just checked the vital functions and they were all right. And the hangover consisted of heavy tinnitus, nausea, ataxia, and dry mouth, and some shivering, periodically for about two or three hours, and the whole experience was resolved in 24 hours. Incidentally, the patient weighed about 95 pounds.

Dr. Cohen: Since the question has been opened, may I ask the audience whether they have records of similar instances, ending in death, or remarkable instances of suicide attempts with Librium.

Dr. Hines: There is a paper in press at the present time which tabulates 31 cases. They all ended uneventfully. As I recall, the highest dose was 1,800 mg. This should appear in the next couple of months.

Secondly, with respect to the oxygenation of the blood, Rosenstein and Kaim of the Coral Gables V.A. Hospital had a paper in press where they showed, in 26 patients who had been studied, that there was no alteration in the oxygen or carbon dioxide carrying capacity.

Dr. Bernstein: I know of a case that I was not actually treating, but at the time I got there about two days after the young woman had made the suicide attempt (I am not sure of the exact dosage, probably less than 100 capsules), no one was called in. Apparently, she went off by herself and "sweated it out." She obviously was ataxic, and was still mildly ataxic when I saw her about 48 hours later; I think she continued on the drug.

Question from the Floor: We have a girl who took 750 mg. I bronchoscoped and eosophagoscoped her, found nothing in the stomach, she was breathing perfectly normally; no treatment was given, and she was all right after 24 hours.

Chlordiazepoxide in the Treatment of Alcoholics

HORACE B. MOONEY, M.D., KEITH S. DITMAN, M.D.,
and SIDNEY COHEN, M.D.

Introduction

Since evaluation is the keynote of this symposium, this presentation will begin with a critical review of the literature on chlordiazepoxide in the treatment of alcoholics. Incidentally, these reports are all of uncontrolled studies. As a contrast in methodology, a controlled, double-blind, out-patient study will be described and its limitations cited.

The Uncontrolled Studies

A summary of the available reports[1-8] is shown in Table I. The reports by Ticktin and Lawrence were the only ones with a fairly large number of patients. By adding all the reports together we find that improvement was reported in 91% of patients treated.

The first large study was by Ticktin and Schultz.[1] They treated 28 acute alcoholics with symptoms of severe anxiety, motor excitement, hallucinations, tremulousness, hostility, confusion, restlessness and even convulsions. They found that 100 mg. of chlordiazepoxide given intravenously in a 1% concentration was usually effective as an initial dose. Relaxation and calming without hypnosis was reported. Some of their patients did fall asleep but according to the authors it was light sleep, and the patients could be easily roused. Mild ataxia and hypotension were the only side effects. Satisfactory results were achieved in 73% of the patients.

The other large study was by Lawrence.[2,9] He treated 145 patients, most of whom had withdrawal symptoms at the start of treatment. Only a few of his patients required hospitalization. The rest of them were treated as out-patients. Daily evaluations presumably were carried out early in treatment. Seventy-eight per cent of his patients had marked relief of symptoms following administration of chlordiazepoxide and complete relief within one or two days. He reported that chlordiazepoxide had a specific action against alcoholic hallucinations and psychomotor restlessness. None of his patients convulsed after chlordiazepoxide was started. Drowsiness and mild ataxia were the only side effects noted. Phenothiazines had been used with considerable success prior to chlordiazepoxide, but it was his opinion that chlordiazepoxide would become the drug of choice in the management of alcoholic psychoses and withdrawal symptoms. He reported that a significantly greater number of patients remained in treatment after their withdrawal symptoms had been treated with chlordiazepoxide than after any prior treatment. The chlordiazepoxide-treated patients were said to be more productive and objective in interviews. Psychotherapy was more meaningful to them. He thought chlordiazepoxide reduced the desire for alcohol and that uncontrolled drinking was less likely to occur. He went so far as to suggest that when the site and mode of action of chlordiazepoxide are determined it would be extremely im-

TABLE I

Librium Treatment of Alcoholics

AUTHOR	Number of Patients	Number Improved	Unimprov. or Worse
Ticktin	28	22	6
Lawrence	145	142	3
Lemere	2	0	2
Rosenstein	1	1	0
Pignataro	1	0	1
Usdin	5	4	1
Breitner	8	6	2
Constant	8	6	2
Total	198	181	17

Total per cent improved = 91%

From the Alcoholism Research Clinic, Department of Psychiatry, University of California Medical Center at Los Angeles 24, California.

portant in determining the etiology of uncontrolled drinking.

Lemere reported four cases of intoxication and mental confusion due to self-medication with chlordiazepoxide. Two of these four patients were described as former alcoholics. He concluded that chlordiazepoxide must be prescribed cautiously for alcoholics and other addiction-prone patients.

Evaluation of the Uncontrolled Studies

Improvement in 91% of patients sounds impressive but does not mean much without a clear idea of the natural course of events. Most patients recover from acute alcoholism and withdrawal symptoms. A faster or better recovery might establish one treatment as better than another, but to prove this, a matching control group is necessary. Studies carried out in a hospital on patients who have been given intravenous medication and then are closely observed have the advantage that many external factors can be eliminated. Also, the severity of the symptoms makes changes more noticeable.

The report by Ticktin and Schultz[1] is strong evidence that chlordiazepoxide has a sedative effect on acutely agitated alcoholics. Whether it is better than phenothiazines or other drugs remains uncertain because a control group was lacking. The claims made by Lawrence[2,9] are difficult to evaluate. He compared the treatment results using chlordiazepoxide with treatment results in a prior period. When experimental studies and comparison studies are separated in time there is always the possibility that other factors may have intervened to account for the difference such as changes in attitudes or approaches, in frequency of appointments, or in selectivity of patients accepted for treatment. Regarding improved productivity, objectivity and meaningfulness in psychotherapy, the way these attributes were measured was not mentioned and the basis for the claim was not explicit. The reported reduction in the pleasure and amount of drinking is unconvincing in the absence of a concurrent control group. The claim apparently was based on patients' reports. For example, one patient said that she had to force herself to take the first two drinks before she was able to obtain the usual pleasurable effects from drinking. This type of statement is typical of alcoholics who find some moral advantage in claiming to dislike alcohol. Such statements are insufficient evidence for a decrease in alcoholic tendencies.

A Controlled Out-Patient Study

A total of 214 alcoholics, nearly all males, between the ages of 26 and 61 years were treated in this study. Approximately 43% of them were seen at a university clinic* and the rest at a charitable service organization** on "skid row." All volunteered readily to participate in an experimental drug treatment program. Some were still drinking; others were in the immediate post-alcoholic or withdrawal state; and the rest had been "dry" for various periods of time. Their alcoholism was of varying chronicity and severity. No attempt was made to select any particular type of alcoholic for treatment.

Dosage and Design

The double-blind procedure was used and the medication was assigned according to a table of random numbers. The patients were seen at weekly intervals and the dose could be raised or lowered within the code number to find the optimum amount. The range of dosage was from 25 mg. to 150 mg. daily. If a patient had been on a previous drug study, two weeks on a known inactive placebo were interposed before beginning the chlordiazepoxide study. Unless there were adverse effects, the medication was given for five weeks. It could be continued

*Alcoholism Research Clinic, University of California Medical Center at Los Angeles 24, Calif.

**Volunteers of America Treatment Center, Los Angeles, California.

longer if there were a good response. Most of the patients terminated treatment themselves by not keeping their appointments which is typical of alcoholics. A hemogram, urinalysis and transaminase test (SGPT) were done routinely at the university clinic at the start of treatment and approximately every third week thereafter. At the "skid row" clinic the tests were ordered when there was a clinical indication for them.

Forms and Procedures

The evaluation procedures were standardized as much as possible. A mood and symptom questionnaire (Form II) was filled out and rated by the patients themselves at the start of treatment and at each weekly visit thereafter. The patients were then interviewed by a research assistant who recorded the reported amount of drug taken and amount of drinking done in the preceding week (upper half of Form I). He also rated them on their grooming, employment status and living quarters. Weight and blood pressures were recorded weekly. A psychiatrist then interviewed the patients and rated them regarding intoxication and symptoms from drinking, facial appearance, several symptoms of disturbed emotionality, sleep disturbance, impaired thinking and unreliability (lower half of Form I). Favorable and unfavorable effects attributable to the drug were rated, and an over-all judgment of the degree of improvement or worsening was made. There was room for progress notes and diagnosis.

On Form I, 0 means unanswered or not applicable; 1 means normal or no symptoms; 2, 3, 4, 5 are gradations of increasing severity up to 6, the most severe degree of abnormality. The rating number for every item was circled in the course of the interviews and the form then served as an IBM work sheet for card punching.

The interviews were primarily evaluative and lasted 10 to 15 minutes, but some psychotherapy, usually of a supportive or persuasive type, was possible. Patients were urged to take disulfiram and many of them did. Joining Alcoholics Anonymous was neither encouraged nor discouraged.

Sensitivity of Evaluative Procedures

At the start we were not sure whether alcoholics would answer this questionnaire any differently from normals. To test the usefulness of the questionnaire, Form II was tried out on supposedly normal medical patients. These were patients at a private medical clinic* who were having an annual physical examination and were not suffering from any serious illness when they filled out the form. The self-ratings of 38 normals on Form II were compared with the initial self-ratings of 87 dry alcoholics. The Kolmogorov-Smirnov Test was used for the comparison. This showed that even dry alcoholics had more severe symptoms on 19 out of 29 items on the mood and symptom questionnaire. Form II had been arrived at after trying several evaluation forms. It was gratifying to find that a considerable number of the items selected helped to distinguish alcoholics from normals.

The next question we had to answer was whether it was possible to get significantly better results with a drug than with a placebo. To test the potentials of these forms, the treatment results of a group of alcoholics who had been given a placebo were compared with the results possible if there were an imaginary ideal drug which would abolish all symptoms within one week. The ideal drug treatment showed a significantly greater degree of improvement than the placebo-treatment in 35 out of 49 items rated on both forms (Form I and Form II). Thus, using these forms and procedures positive findings would be possible and numerous if there were an ideal treatment. It was hoped that there would be at least a few positive findings if a drug were reasonably effective.

*Redondo Beach Medical Clinic.

Data Analysis

When our study was completed the code was broken and the results analyzed with the help of a computer* and a program** written for such studies. The initial ratings of the drug- and placebo-treated groups were compared to test the fairness of the matching. The total population and the "skid row" group considered separately were matched. The university clinic patients were mis-matched in that the pla-

*IBM-709, Western Data Processing Center, University of California at Los Angeles, Calif.
**QUAP-4 by John R. B. Whittlesey.

FORM I—DRUG STUDY

Date.....

Name..... Last Drug & Code.....

Interviewer's Record
Dose of last drug.....
Pills given.....
Pills left.....

	Name					Card	Date			Drug		New Old	Antabuse Taken
						1							
	1	2	3	4	5	6	7	8	9	10	11	12	13

Explain New or Missed Appts. (work, jail, health, Rx attitude).....

14. Approx. Time Last Visit
0. Unknown
1. Start
2. Less than wk.
3. One week
4. 2 weeks
5. 3 weeks
6. 4 weeks
7. More

15. Avg. Dose Tkn. Past Week
1. 3x
2. 2x
3. **Std.** dose
4. 2/3–3/4
5. 1/2 **Std.**
6. 1/4–1/3
7. None/N.A.
8. Other
9. Irreg.

16. Days Since on Drug
0 1 2 3 4 5 6
7 8 (more) 9 unk

Wks. on Drug 17 18

19. Seen at
0. Unknown
1. Vol. of Am.
2. UCLA
3. Tel. Vol./Am.
4. Tel. UCLA
5. Priv. Off.
6. Other.....

20. Reason Missed
0 Didn't
1. Better
2. Working
3. No help
4. Unable to come
5. Forgot
6. Other Rx.....
7. Drinking
8. Jail
9. Worse on drug
X. Other.....
Y. Unknown or N.A.

CODE
0. **Unknown**
1. **None**
2. **Minimal**
3. **Mild**
4. **Moderate**
5. **Severe**
6. **Very Severe**

21. Shabbiness
0 1 2 3
4 5 6

22. Unemployment
0 1 2 3
4 5 6

Address:
Tel. No.

23. Days Drinking Past Week
0. Unknown
1. None
2. 1–2
3. 3–4
4. 5–6
5. 7

24. Deg. of this Drkg.
0 1 2 3
4 5 6

Days Dry

25. Abode
0. Unknown 6. Outdoors
1. Own
2. Apt.
3. Room
4. Brdg.-Half-Way
5. Movie/Flop-room

Doctor's Record: How do you feel today?.....

How have you been (on last drug)?.....

26. Pres. Deg. Intoxication	27. Symp. from Drinking	28. Morbid Facies	29. Anxiety/Agit.	30. Depression	31. Lack Energy
0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6

32. Insomnia	33. Day Drowsiness	34. Elation	35. Impaired Thinking	36. Hostility/Irrit.	37. Unreliability
0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6	0 1 2 3 4 5 6

38. Favorable Effects of Med.
0. N.A. 3. Good 4. Fair
1. Excel. 5. Slight
2. Very Good 6. None

39. Adverse Drug Effects
0. N.A. 4. Mod.
1. None 5. Severe
2. Min. 6. Very Severe
3. Mild

Specify.....
Notes (lab. etc.).....

40. Main Dx.
0. Unknown 5. Alcoholic 6. Inadequate
1. Normal 7. Borderline
2. Neurotic 8. Schizophrenic
3. Immat.-dep. 9. Organic
4. Sociopath X. Other.....

41. [ ] **Summary of Drug Effects** 42. [ ] **Dr.**

Target Symptoms and Progress:.....

Wt.....
BPL...../.....
BPS...../.....
BPS...../.....

Other medication being taken.....Antabuse given.....Vitamins.....

New drug.....Code No.....No. Tabs.....Dose.....

cebo-treated patients had more severe symptoms on several items. For this reason, the university clinic drug-treated group was also compared with a matching large placebo-treated group from five previous studies, in which the same forms and procedures were used.

The return rate for the total population was poor as usually is the case with alcoholics, but it was consistently better for those who received chlordiazepoxide than for those given the concurrent placebo or any of the previous drugs or placebos we have tried (Figs. 1 and 2).

The difference in the return rates did not appear to be related to any of the initial ratings on our forms. For example, since chlordiazepoxide is a tranquilizer we thought there might be an improved return rate among those who were anx-

FORM II

Name ..... Age .....Date .....
Last First Middle

Answer the questions below to show how you have been feeling this past week
(Circle only one answer for each question) Comments

43. I am troubled by poor appetite	1. No	2. A little	3. A lot	4. Extremely
44. I crave alcohol	1. No	2. A little	3. A lot	4. Extremely
45. I have difficulty sleeping	1. No	2. A little	3. A lot	4. Extremely
46. I'm tired during the day	1. No	2. A little	3. A lot	4. Extremely
47. I feel restless	1. No	2. A little	3. A lot	4. Extremely
48. I have the shakes	1. No	2. A little	3. A lot	4. Extremely
49. I feel light-headed or dizzy	1. No	2. A little	3. A lot	4. Extremely
50. I have trouble thinking clearly	1. No	2. A little	3. A lot	4. Extremely
51. I feel sick to my stomach	1. No	2. A little	3. A lot	4. Extremely
52. My sex life is unsatisfactory	1. No	2. A little	3. A lot	4. Extremely
53. My heart races	1. No	2. A little	3. A lot	4. Extremely
54. My future looks black	1. No	2. A little	3. A lot	4. Extremely

This Past Week Were You in General:

55. Sluggish	1. No	2. A little	3. A lot	4. Extremely
56. Unsociable	1. No	2. A little	3. A lot	4. Extremely
57. Excitable	1. No	2. A little	3. A lot	4. Extremely
58. Unreliable	1. No	2. A little	3. A lot	4. Extremely
59. Elated	1. No	2. A little	3. A lot	4. Extremely
60. Impatient	1. No	2. A little	3. A lot	4. Extremely
61. Oversensitive	1. No	2. A little	3. A lot	4. Extremely
62. Worried	1. No	2. A little	3. A lot	4. Extremely
63. Depressed	1. No	2. A little	3. A lot	4. Extremely
64. Nervous	1. No	2. A little	3. A lot	4. Extremely
65. Lonely	1. No	2. A little	3. A lot	4. Extremely
66. Shy	1. No	2. A little	3. A lot	4. Extremely
67. Irritable	1. No	2. A little	3. A lot	4. Extremely
68. Fearful	1. No	2. A little	3. A lot	4. Extremely

[ ] + [ ] + [ ] + [ ] = [ ]

69. In general the past week, did you feel: 1. **Fine** 2. **Fair** 3. **Pretty bad** 4. **Terrible**

70. Do you think you felt: 1. **Better** 2. **No different** or 3. **Worse** this week as compared with the week before

71. **Comments** [ ] .....

.....

.....

72. **Interviewer** [ ] ..... 73. [ ] 74. [ ] 75. [ ] 76. [ ] 77. [ ] 78. [ ] 79. [ ] 80. [ ]

ious at the start of treatment, but such was not the case. Nor did treatment results explain the difference in the return rate. When the total population was considered, the treatment results with chlordiazepoxide were no different than with the placebo at any point during the first five weeks. After that, there were too few patients remaining to make a comparison. When the "skid row" population was considered separately, those given chlordiazepoxide showed greater improvement in the total score of the patient-rated mood and symptom questionnaire after one week of treatment but only then. The comparison of the university clinic drug-treated group with the placebo-treated group in five previous drug studies showed that the patients who received chlordiazepoxide were rated by the psychiatrists as consistently showing more favorable effects from the second week of treatment onward. This difference was sufficient to reach statistical significance after the second and fourth weeks of treatment (nominal .025 and .01 levels). Counteracting this was the finding that the patients also showed more side effects at the same time. These findings are weakened by the fact that the controls used for this comparison were not concurrent, i.e., had been taken from previous drug studies, and there is the possibility that some factor other than the drug treatment accounted for the difference.

To find indications for chlordiazepoxide, the initial ratings for those patients who improved on the drug were compared with those who did not improve. Those judged by the psychiatrists as improved had rated themselves as more unsociable at the start of treatment, otherwise the starting ratings were essentially the same. In contrast, there were no positive indications for the placebo, and among the placebo-treated patients those who were judged to be unimproved were more shaky, wor-

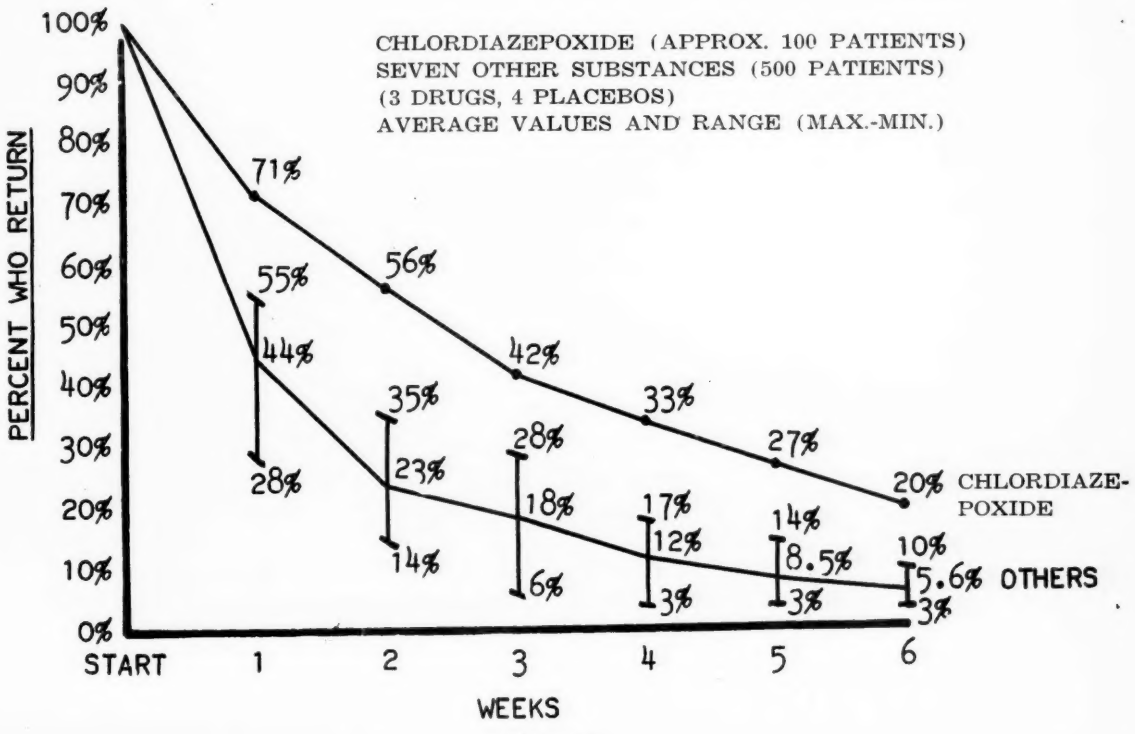


Figure 1.

EFFECTS OF DRUG TREATMENT ON RETURN RATE OF OUT-PATIENT ALCOHOLICS

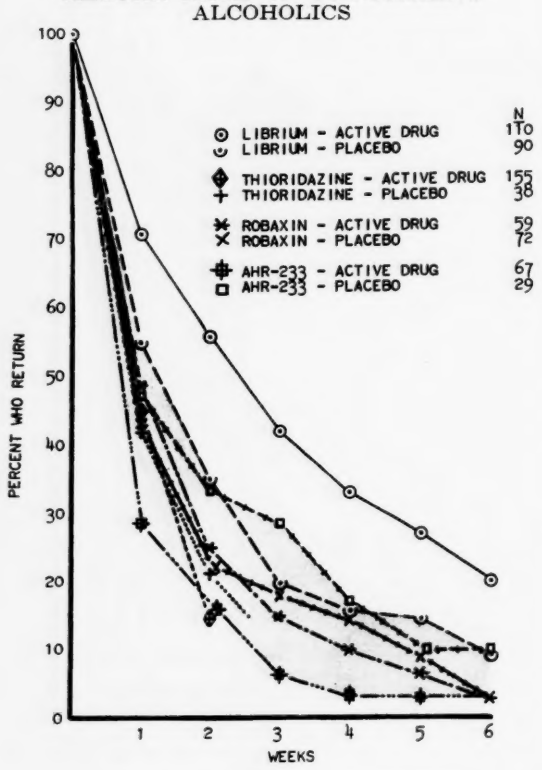


Figure 2.

ried, shy and fearful at the start of treatment. These findings suggest that if a population of alcoholics with marked anxiety had been selected for treatment a more noticeable difference in the results might have been obtained.

Side effects were greater for the drug-treated patients. These included drowsiness, ataxia, sexual disturbance, and dizziness. After four weeks of treatment the patients who received the drug showed a tendency to gain more weight than those who received the placebo. There were no alterations in blood pressures, liver function tests, hemograms, or urinalyses that could be attributed to the drug.

Evaluation of the Controlled Out-Patient Study

A controlled, double-blind study has serious limitations too. Modell[10,11] has likened the controlled drug study to balance scales with the placebo treatment on one side balanced against the drug treatment on the other side. A significant shift in the pointer of the scales will indicate which treatment is better, but the scales may be very insensitive and increased friction due to dead-weighting may render them practically useless. In the field of psychopharmacology, the scales are rather crude observations and ratings which are certainly not specific for drug action and may even be insensitive to it. The value of reports on questionnaires decreases with the time interval between observation and report. When weekly appointments are made, it is doubtful if a patient can give an accurate account of how he felt for the entire past week. The questionnaire also suffers from problems of patient comprehension. Form II was purposely made very simple but there is still difficult to devise a questionnaire which some doubt as to whether some of the "skid row" patients understood all the words in it. In addition, words have multiple meanings and connotations. It is is not ambiguous in some respect. Psychiatrists' opinions and ratings are also far from being exact units of measurement.

Dead-weight according to Modell's analogy makes the balance scales less sensitive. In our study, dead-weight also means all those factors other than the drug which can influence the ratings on Form I and Form II. Unfortunately, these factors are enormous in out-patient drug studies with alcoholics. Placebo effects probably account for a high proportion of favorable reports, especially with alcoholics who are highly suggestible. It should be remembered that the phenomena of the placebo effects are on both sides of the balance scales, not just on the side with "the placebo." Then there is the problem of bias by the doctor who wants his patients to get well and is prone to see improvement even if he does not know whether his patient is getting a drug or a placebo. Patients also are biased. They want to improve and in fact expect to improve. With

clinic-treated alcoholics there is the added problem of obsequious patients trying to please the doctor by reporting improvement when there is none. Then there is a large group of external factors particularly among "skid row" alcoholics. A place to sleep at night, a square meal, a job, a return to the family, or a court sentence can produce tremendous changes in emotionality and general outlook, and these are reflected on the rating forms which we are using to evaluate drug action. To complicate things further there is the fact that patients who seek treatment usually do so when their symptoms are most severe and if they return at all probably will be better no matter what treatment was given. It is possible that the return rate itself may be selective for those who improve. None of these factors are eliminated by a controlled study. By randomization and by testing for mismatching of the items rated, it is hoped that the dead-weight factors will at least be equally balanced on both sides of the scales. A negative report in a controlled drug study therefore does not mean that the drug in question has no effect. It means that the drug effect was not sufficient to produce a noticeable difference in the presence of the dead-weight factors and with the subjects and instruments used.

Keeping these things in mind what can be said about the controlled drug study just reported? It is apparent that when a heterogeneous group of out-patient alcoholics are treated with chlordiazepoxide and evaluated at weekly intervals using a symptom questionnaire and brief clinical interview to measure changes, the drug effect could not overcome the dead weight factors sufficient to make a noticeable difference. The only exception to this was the return rate which was better among those who receive the drug. The explanation for this must lie in some factor not assessed by our evaluative procedures.

Conclusions

The uncontrolled drug studies suggest that chlordiazepoxide may be of value in the treatment of acutely disturbed alcoholics and withdrawal symptoms, but a controlled in-patient study needs to be done to substantiate the claims that it is better than other drugs currently available. Except for an improved return rate, a controlled out-patient study produced little convincing evidence that chlordiazepoxide alters the natural course of events for the alcoholic. The limitations of the controlled and uncontrolled studies were cited, indicating that techniques for the clinical evaluation of drug effects must be refined. Extraneous factors must be minimized as much as possible; efforts to obtain homogeneity should be made; and the instruments for measuring change must be improved.

Methodology and Psychological Tests in the Evaluation of Chlordiazepoxide

HARRY GRAYSON, PH.D.*

In the quest for improved psychopharmacological agents of broad treatment scope, maximum potency, and minimum toxicity, Librium, a new drug which is reported to be unrelated to other tranquilizing or energizing agents, has been developed. This paper concerns itself solely with the methodological aspects of research in the evaluation of the drug. A discussion of research methodology in chemotherapy will therefore be presented as a background against which the published researches can be examined and the present status of Librium ascertained.

Librium, as any new drug, must undergo at least three qualitatively different stages of research investigation before it may rightfully take its place in the therapeutic armamentarium. These stages are: 1) preliminary laboratory screening in animals; 2) exploratory or uncontrolled clinical investigation in humans; and 3) confirmatory or controlled research, preferably of an interdisciplinary nature.

Preliminary screening studies in animals are performed in order to obtain information regarding potency, physical and behavioral toxicity, functions affected, and mode of action. From these animal studies, inferences regarding therapeutic potentialities and toxic possibilities in human subjects are drawn. If the findings are encouraging, the drug is deemed suitable for clinical trials; and the pharmacological and toxicological data are made available to the clinical investigator. However, even the best and most extensive animal pharmacological data provide only clues as to the therapeutic potential and only partial protection against unexpected and potentially-serious reactions in humans. Therefore, exploratory clinical studies are necessary in order to establish dosage limits and optimal levels; to watch for human toxicity, side reactions, and contraindications; to observe the kinds of patients, symptoms, or syndromes which appear to respond favorably to treatment; and, on the basis of all this, to decide whether the drug appears to be sufficiently "promising" to warrant more intensive and exacting study.

The exploratory stage is one of discovery, of following-up clues, of pursuing hunches. It is characterized by a degree of flexibility and freedom to shift, as new ideas suggest themselves, on the basis of clinical observations. Trial and error procedures, kept within reasonable bounds of safety, and consistent with the therapeutic clues furnished by the animal-screening studies, are appropriate and desirable, in order to open up leads which may then be pursued under more scientifically rigorous conditions. The exploratory studies thus provide direction for more controlled researches and assist in the crystallization of subsequent experimental design. For example, among other things, they may help to determine which types of patients to select for study, and the dosage levels to be prescribed, the nature of the therapeutic gains to look for, and the kind of toxicity tests to employ.

Finally, confirmatory, rigorously-controlled research studies are necessary in order to check out, in fairly conclusive fashion, the degree of therapeutic efficacy. Among the procedures utilized in confirmatory studies are: utilization of appropriate controls; employment of objective evaluation procedures of ascertained reliability; compliance with statistical requirements; and the strictest effort to rule out or take into account the operation of factors other than the drug under

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investigation which may contribute toward the results obtained.

In a report published by the Group for the Advancement of Psychiatry appears the following statement: "The conclusions reached in an exploratory study claim less than conclusions reached in a confirmatory study. The exploratory conclusion says, in effect, 'There is some evidence for this finding; it is worth considering; it needs more investigation.' The confirmatory study claims more. It says, in effect, 'This finding is very likely correct; it has been checked with exceptionally great care; your confidence in it is justified, and you have a full warrant for your belief.' "[1]

Every research stage has its distinctive role, purpose and importance. From a scientific point of view, until all stages have been satisfactorily accomplished, the drug, perforce, remains on investigative status.

Unfortunately, it is not unusual for exploratory-type studies to come up with highly promising indications which confirmatory-type studies later fail to substantiate. Perhaps the following quotation partly accounts for this phenomenon. "To those of us who engage in medical research, it often seems as if Nature were laying traps on every hand, to prevent our researching the truth. . . We are extremely aware of Nature's trap-laying habits and of the human tendency to deceive oneself by the desire for positive and important results from one's research."[2]

These traps are so numerous and varied that the achievement of valid findings is indeed a difficult accomplishment. In order to furnish some idea of the kinds of traps besetting the path of the research investigator, I have classified them into three broad categories and shall give some examples of each.

The first category is that of "psychological traps." One is "projection" or a tendency toward seeing favorable results which are not there. The enthusiasm of a research investigator has often been blamed for the exaggeration of positive effectiveness of a form of treatment. Another is "repression," or failure to see unfavorable results. The investigator's emotional investment in his research sometimes makes it difficult for him to face evidence to the contrary. A third is "distortion" or interpreting unfavorable or neutral results as though they were favorable. The ensuing "gobbledegook" and semantic gymnastics sometimes employed in distortion is a tribute to the ingenuity of the unconscious.

Another is that of "unconscious experimenter bias" which may result in innocently "stacking the cards" in such a way that desired outcomes emerge. In addition, there is the trap of "displacement," or attributing to the drug under investigation effects which are really produced by other factors operating both from within and outside of the specific research situation.

Additional psychological traps arise out of such factors as: humanely motivated wishful thinking on the part of the treating physician; and out of a desire on the part of the patient to get well, or to please the physician, with consequent role-playing of improvement which is not really there. Not to be over-looked, of course, is the powerful effect of suggestion on both patient and physician.

The second category may be termed that of "logical and technical" traps. An example is the "post-hoc fallacy"—that because a patient improved while on the drug, therefore, he improved because of the drug. Often-times, the observed improvement is a result of concomitant changes in the life situation of the patient rather than a result of the medication.

Related to this is what might be called the "percentage" fallacy: that the percentage of patients showing improvement while on a drug improved because of that drug. In any group of patients, there is a greater or lesser percentage of so-called "placebo-reactors" who respond favorably even to inert substances.

Another example is that produced by

practice effect. A patient may show improvement on psychological tests administered before and after treatment, or on psychiatric rating scales, not necessarily because of the treatment, but because he has become more familiar with taking tests, or because the psychiatrist has become more adept in the use of rating scales.

The semantic error is another logical trap and involves, in one way or another, a misuse of language. For example, to imply that a drug was evaluated for ten months because the experiment was conducted for ten months—when, in fact, no individual patient received the drug for more than two months, is to be guilty of committing a semantic error. It is the duration of medication for the patient that matters, and not how long it took the investigator to obtain the patients for his study.

Other logical and technical traps which hound the researcher include: utilization of biased patient samples; misuse of statistical data; and over-generalization of conclusions. Included in this category are such errors as drawing confirmatory-type conclusions on the basis of an exploratory study; or assuming that valid final conclusions relative to the effectiveness of a drug can be reached by pooling a sufficiently large number of exploratory-type studies. The third and last category may be referred to as "sociological" traps. One of these grows out of the "pioneer urge" —to be the first to prove that a brand new hitherto-unused drug or treatment procedure is therapeutic. This "pioneer urge" brings into play almost all of the psychological traps alluded to earlier, and perhaps some that have not yet been identified. The usual tendency is for the first investigator to find that a drug works.

Another, which dulls the critical faculties of the research investigator, and provides recognition without perspiration, may be called the "bandwagon" trap. After a number of research articles have appeared, which purport to find a drug effective, the investigator feels a lessened sense of urgency to be careful in his observations, and joins the bandwagon. One writer notes: "We need to explicitly recognize this difficulty; in our haste to confirm our clinical observations, we sometimes present very tenuous proof, usually terming it a trend or tendency. Unfortunately, as in the childhood game of 'Gossip,' these trends tend to appear as confirmed facts as they are repeated from author to author, or even from the sections on results to discussion to summary, in the same article."[3]

Other traps grow out of the total sociological setting in which the research takes place. For example, the drug company frequently provides the drug "gratis" to the investigator. Although this is commendable, and even necessary, in order to further research, the investigator may consciously or unconsciously feel a sense of obligation to show that the drug is effective.

With these and other traps surrounding the research investigator, the problem of arriving at a truthful evaluation, so that a useful drug is not discarded, nor a useless one retained, is indeed a difficult one. Exceptional care is necessary in the final research stage to design the studies in such a way as to minimize or control the operation of traps which may lead to invalid findings and erroneous conclusions.

The ultimate test of the efficacy of a drug is its ability to pass successfully through the confirmatory stage of research. This involves scientific verification of the clinically-promising findings revealed in the exploratory studies. Confirmatory studies will often utilize blind controls in order to avoid possible contamination of patient behavior or of clinical judgment. The use of placebo by a research investigator is not an adequate control if the physician making the clinical judgment knows which patients are receiving drug and which are receiving placebo.

In the so-called double-blind study, for

example, none of the direct participants—neither the investigator, nor the staff, nor the patient—knows who is getting the active drugs and who is getting an identical placebo. The attempt here is to avoid both verbal and non-verbal communication of the knowledge of who is getting the drug. Even this may be insufficient, particularly in connection with drugs which may produce side reactions, for these may serve as tell-tale clues as to which patients are receiving the active drug. So-called "disguised" placebos, producing side reactions such as drowsiness, which frequently accompany the use of phenothiazine compounds, have, therefore, been utilized in some studies.

The use of appropriate placebo controls as a basic requirement of confirmatory research cannot be overemphasized. Every drug has what might be called a "built-in" placebo effect which must be discounted if we are to attribute the drug's effectiveness to its chemical structure. For example, cases have been reported in double-blind studies in which the patient's ward physician was most eager to know what drug a particular patient had received and to which he had responded so well, only to find that the patient had been on placebo.

One investigator described a study with which she had been in contact where the new drug had effectively calmed all the patients getting the drug on a single ward. Supplies of the drug ran out, and all the patients became worse. Then a placebo, which the staff believed to be the active drug, was given and all the treated patients became calmed again. Undoubtedly, had the active drug been reinstituted, this calming effect would have been attributed to it.

Well-documented studies have been reported in which the placebo has been effective in treating fairly high percentages of patients suffering from a wide variety of conditions, including anxiety, muscle tension, restlessness, irritability, severe cardiac, arthritic and post-operative pain, headaches, motion sickness, gastric hyperacidity, coughing and symptoms of the common cold. In one study, definite changes in functioning of the autonomic nervous system were found in a placebo-treated control group of chronic schizophrenic patients.[3] Furthermore, toxic placebo effects, as real as those produced by any genuine drug, including drowsiness, mental confusion, nausea, faintness, and diarrhea have been recorded by many investigators in the field. In a test conducted by Stewart Wolf, three of 31 patients became violently ill. "One of the three," he recounts, "had sudden overwhelming weakness, palpitation, and nausea within fifteen minutes of taking her tablets. In a second patient, a diffuse itchy, erythematous maculopapular rash developed after ten days of taking placebo pills. A skin consultant considered the eruption to be a typical dermatitis medicamentosa, or drug-induced reaction. After use of the pills was stopped, the eruption quickly cleared. In a third patient, within ten minutes of taking her pills, epigastric pain developed, followed by a watery diarrhea, urticaria and angioneurotic edema of the lips." In an evaluation of streptomycin as an adjunct to chest surgery, two-thirds of a group of patients who received only placebos developed every sign—including blood-cell changes and hearing loss—of streptomycin toxicity. And one investigator has reported a case in which a lactose placebo brought about a shattering impairment of liver function.

The implication of these toxicological placebo findings would be that many cases of reported side reactions from drugs are improperly attributed to the drug per se. Similarly, many cases of reported improvement from drugs may be improperly attributed to the drug per se.

In order to ascertain the present status of Librium for this Symposium, 31 articles,[5-35] which appeared in the literature, were reviewed. Of these, two reported the results of experimental screening trials with animals; two were highly favorable

summary reviews of the findings of other studies; and twenty-seven were reports of studies with patients, including hospitalized patients, prison patients, out-patients, and private patients suffering from the full range of psychoneurotic, psychotic, psychosomatic and psychopathic conditions, as well as seizures, alcoholism, cardiovascular disorders, and persistent muscular restlessness.

It is not feasible to review these studies in detail, but certain features may be noted. For example, out of the 27 studies with human subjects, only one purported to be a controlled investigation. The remaining 26 articles, six of which had the word "preliminary" appearing in the title —and many others had it in the body of the report—were all reports of uncontrolled, exploratory-type studies.

Although in several studies large numbers of patients were carefully observed, and in a number of studies interesting and dramatic case reports were presented, and in some studies insightful clinical acumen was clearly discernible, and in all studies the personal integrity of the investigator remains unquestioned, the studies, nonetheless, must be classified as exploratory studies, and subject to their inherent limitations and fallibilities.

Comments like the following, which appeared in some reports, were equally applicable to others. "No attempt was made to control a variety of variables which might have influenced the outcome of treatment"; or, "The series of cases reported is small and makes no pretense of being controlled."

One enthusiastic investigator reported, "Librium produced a cessation of the symptoms of anxiety or its direct equivalents—panic, agitation, globus hystericus, stress-related headaches, nausea, dysphagia—in one hundred per cent of the patients. Such a percentage," he continued, "may seem to indicate a need for more careful observation, or, possibly, a neurotic need on the part of the investigator that all his patients recover."

Another investigator wrote: "This drug relieved both psychic and somatic symptoms in all of sixty-five patients treated." Another stated: "In this preliminary trial, 44 of 45 disturbed patients—including several schizophrenics—were afforded relief." This last investigator mentioned that 25 patients under treatment with Librium also received electroconvulsive therapy in the office.

One investigator commented: "In a simple clinical study of this kind, it would be inappropriate to make a detailed analysis of the results." Nevertheless, in the summary, he concluded that the drug "is effective in reducing anxiety and tension, chiefly in neurotic patients."

All studies reported Librium to be effective for practically every type of patient treated, with a few exceptions noted in some reports. Many expressed outright enthusiasm for the drug. Various side effects were reported by some investigators, and none by others. The percentages of over-all improvement reported ranged from 53 per cent improvement in one study to 100 per cent, in two studies. The median over-all percentage of improvement was 80 per cent. Different percentage improvement figures were reported for different diagnostic groups; and different studies, as would be expected, reported differing percentages of improvement for the same diagnostic groups. The number of patients observed in the different studies ranged from one patient to 494 patients, the median number of patients being 65. The ages of patients ranged from 9 to 80 years. Length of illness ranged from 2 months to 44 years.

Incidentally, in none of the studies was there any attempt to break down improvement ratios for different age groups or for patients with different lengths of illness, or even by sex, even though there were different figures recorded for male and female patients.

In the various studies on Librium which have been published, the improvement fig-

ures cited in connection with the treatment of anxiety and tension, control of agitation, obsessions and phobias, usefulness in neuroses, psychoses and chronic alcoholism, and alleviation of tension associated with gastrointestinal, cardiovascular, gynecologic and dermatologic disorders is impressive. But the following limitations of the studies should be kept in mind:

1. Except for one example of a controlled study, which was based on very few cases and reported in a most sketchy fashion, all of the studies were of the exploratory type. Not a single study utilized a placebo, or other drug, or no-treatment control group, although one obtained patient preferences for Librium versus for three other drugs.

2. Only one study utilized psychological testing, and this involved a single test, the Minnesota Multiphasic Personality Inventory. This study failed to use a control group which might have controlled for practice effect and other factors.

3. In every instance, the person making the clinical judgment knew that the patient was on a new drug, and, in a number of instances, the patients were similarly informed. This situation is most conducive to the operation of the various psychological traps which have been discussed.

4. In several studies, the drug effects were contaminated by the presence of concomitant therapies, such as psychotherapy or convulsive therapy.

5. Not a single study made use of clinical judgments of the same patient by two independent observers. Thus, in no study is the reliability or consistency of judgments known.

6. In very few studies did the investigators define the terms used to express different degrees of improvement; all others merely mentioned degrees of improvement such as improved-unimproved, or excellent—good—fair—poor, without defining them, leaving the decision up to the leniency or strictness of the judgment of the particular observer. Furthermore, the standards of judgment varied in different studies. Thus, in one study "slight relief" was considered as acceptable improvement, while in another study a "fair" response was considered as unsatisfactory improvement.

7. The term "improvement" was rarely specified in terms of therapeutic goals, such as symptomatic relief, increased responsiveness to other therapies, specific cure, social rehabilitation, better hospital adjustment, or improvement in the anxiety-tension component, thus leaving its meaning vague in many studies. For example, the fact that a previously disturbed patient may be much quieter may denote real improvement to a ward attendant who spends eight hours of each working day in a ward with chronically disturbed patients. To a supervising psychiatrist, this same change might signify a further retreat on the part of the patient and less accessibility to a therapist.

8. In several reports, there was some discrepancy between the data presented and the conclusions drawn. An example is the following quotation: "Librium was found to be remarkably effective in thirty of the forty-three patients treated, the response being excellent in eight and good in twenty-two."

9. A number of exploratory reports drew confirmatory-type conclusions. For example, one investigator said that "Librium is the most potent agent presently available in its ability to allay anxiety and tension in the presence of depression." Another stated that Librium "represents the most significant advance to date in the pharmaceutical treatment of anxiety states."

10. Although it is considered proper procedure to quote previous studies, the totally uncritical attitude and complete acceptance of the findings and conclusions of other investigators suggests that the "bandwagon" trap was in full operation. One writer actually stated with regard to his own study: "It is acknowledged that such categorization is readily open to at-

tack, subjective and unscientific, vulnerable because of multiple variables not defined. The writer can only plead expediency for the purposes of this preliminary report . . . submitting that the findings are usefully indicative and consistent with those reported by other clinicians from their initial experience with Librium."

In conclusion, I think it has been made abundantly evident, on the basis of the exploratory studies which have been reported in the literature, that Librium has successfully passed the second research stage and may indeed be considered as a promising drug worthy of further intensive investigation.

It is now time for the third stage, confirmatory-type research studies to be undertaken. For, until such confirmatory controlled studies utilizing placebo or a comparison drug are conducted with randomized patients under "blind" conditions, with adequate evaluative criteria, no final scientifically-based judgment on the efficacy of Librium is possible. I pass this on as a recommendation to the Hoffmann-La Roche Company and to interested investigators.

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The Effects of Librium in Psychiatric Disorders

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After the introduction of a new drug into clinical practice a number of stages commonly occur in its evaluation. In the first stage, there is restrained enthusiasm consistent with medical and scientific caution. The second stage often shows a less restrained enthusiasm, and a flood of approving papers appear. Statements such as, "a most valuable agent," "specific against anxiety and tension," "successful treatment of patients refractory to other modalities of therapy" are noted in publications, and expressions appear, such as "significant therapeutic success," "effect on behavior, social adjustment . . . and evidence of renewed interest in life were remarkable." In the third phase one begins to notice papers with a more cautious tone. Some failures to confirm results in double-blind studies appear, and side effects also begin to appear more prominently, as well as complications. In the fourth phase we begin to read pleas for the judicious use of the drug in selected cases, and articles inveighing against the indiscriminate use of an as yet unproven drug. Following this there is delineation of the type of cases where it might be useful. And finally, it is discovered that its main effect is to facilitate psychotherapy. There is, of course, considerable overlapping in these phases, and some of them are inevitable in any scientific program of study. It is important for us, however, to carry on a continuous evaluation during each phase of investigation and to evaluate critically not only those publications which are very enthusiastic but also those papers which repudiate the favorable results obtained by others.

The investigations on the drug chlordiazepoxide (Librium®) are briefly reviewed and a description is given of the results claimed by investigators. In order to partially obviate early enthusiasms, the authors' claims have been presented, but have also been recalculated to include among the improved only the upper two grades. For example, if "excellent," "good," and "fair" were the categories, only "excellent" and "good" were included. Some of the reports involved only two categories, "improved and unimproved," the former probably including some of the "fair" results. The comparison of the two sets of figures is given in Table I.

Based on these reports a great deal of enthusiasm for this new medication is understandable. It will be noted, however, that the references cited are not controlled studies. In an apparently controlled study reported by Walzer, Kurland and Braun[17] it was indicated that 55% of 40 patients in all diagnostic categories had marked and sustained reduction of anxiety, but other symptoms were not affected. There was a slight relief of tension in 33% of obsessive-compulsive patients and moderate improvement in one of four phobic patients. They noted side effects such as hostile or aggressive acting-out, sensitivity to alcohol, and episodes of violent destructive behavior (4 patients). Notably they stated that depressions did not respond to Librium. They summarized by saying that the drug appeared to be most beneficial for anxiety arising from anxiety neuroses, but that its effect on anxiety in other psychiatric conditions was more limited, variable and unpredictable. Its influence on other symptoms was minimal. Smith[18] reported on a controlled study of 45 patients, mostly chronic schizophrenics, one-third of whom received Librium. Improvement occurred in 53.2% (20% using upper two grades of improvement). In a further non-blind study on 143 patients, including 87 chronic schizophrenics, he found various grades of improvement in

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TABLE I

Comparison of Author's Reported Figures and Recalculation on Basis of Two Upper Grades of Improvement

AUTHOR	Author's % improvement	Recalculated % or author's figures of upper two grades of improvement	COMMENTS
TOBIN et al.[1]			
psychiatrist's evaluation	81	70	
patient's evaluation	84.5	37	
BOWES[2]			Does not give figures. States that with 200 patients treated, he has been convinced that "Librium represents the most significant advance to date in the psychopharmaceutical treatment of anxiety states."
KINROSS-WRIGHT[3]			
neurotic	77		Has only 2 categories—improved, unimproved.
personality disorders	84–100		
schizophrenics (private office)	57		
schizophrenics (total clinic and prison patients)	30		
private office patients	67		
clinic outpatients	64		
prison center patients	53		
FARB[4]			
psychiatric disorders (including several schizophrenics)	98	38	Broad spectrum of psychiatric disorders.
BREITNER[5]			
psychiatric disorders	80	73	Wide variety of psychiatric states.
CONSTANT[6]	90	65	Wide variety of nosological conditions. Decidedly beneficial in depressions.
TICKTIN & SCHULTZ[7]			
acute alcoholism	73–85		Used the drug as a quieting agent for hyperactive, alcoholic and psychotic patients.
acutely disturbed neurotics, psychotics	Some success		
SUSSEX[8]	76		21 patients, 6 of whom had schizophrenic admixtures.
BERKWITZ[9]	90		51 patients in various diagnostic categories. Observed an excellent response in 33%, and an over-all good response in 90%.
USDIN[10]	70		80 patients with a diversified group of symptoms including psychoses, personality disorders and pseudoneurotic schizophrenics.

AUTHOR		Author's % improvement	Recalculated % or author's figures of upper two grades of improvement	COMMENTS
FRAIN[11]				
		79	40	169 chronic psychotic patients of whom nearly two-thirds were schizophrenics.
PIGNATARO[12]				
		80	67.5	Private psychiatric practice.
TOBIN and LEWIS[13]				
Objective evaluation based on 212 patients	psychoneuroses	85.7	64	212 patients.
	affective reactions	77.4	51	
	pseudoneurotic schizophrenics	72.7	50	
Subjective improvement of directly perceived anxiety in 177 patients	psychoneuroses	91.3	48	
	affective reactions	95.2	62	
	pseudoneurotic schizophrenics	78.9	50	
Subjective response of specific symptoms (phobic reactions, obsessive thinking and compulsive behavior, depression, tension, lethargy, physical concomitants, conversion reactions, hysterical acting-out behavior)		78.2–94.8	12–56	
Objective evaluation of over-all improvement of total 212 potients		80.2	59	
Subjective improvement in 177 patients with directly perceived anxiety		87.6	48	
PERNIKOFF[14]				
		100	95.4	Utilized Librium in treatment of myalgias and arthralgias, psychoneurotic disorders, cardiac patients. Psychic and somatic improvement occurred in most symptoms, including pain, anxiety, headache and inflammatory processes.
STANFIELD[15]				
		74		150 patients. Drug found to be effective in anxiety states, psychophysiologic reactions (when mild), situational reactions, and to a lesser extent, character disorders. Other medications were used concurrently in this study.
ENGLISH[16]				
				87 patients. No figures given. Librium "without exception," produced improved control.

74.7% of schizophrenics, 54.8% of acute psychotics, and 60% of the psychoneurotic group.

Librium has been used by the author in private office practice, both in patients who were in intensive, interpretive psychotherapy and in patients who were receiving a more supportive type of therapy. Observations of the patients came from three sources: 1) a questionnaire filled out by the patient with a subjective evaluation, 2) a questionnaire with the more objective evaluation of the therapist, and 3) the close observation of the patient in many cases, in the interpersonal relationship of intensive psychotherapy.

The response in two patients appeared to be quite satisfactory. The first was a 43-year-old woman who developed phobias about being alone dating from an incident 12 years before, in which a paper hanger beat her with a roll of paper, incident to a rape attempt. Since that time she was alone only on extremely rare occasions, and her whole life was built around this phobia. She was in psychotherapy with three different therapists almost constantly since that time. In addition to the phobia she felt depressed, weak and faint, was unable to drive a car and had considerable insomnia. Psychotherapy of an interpretive type was not very helpful, although supportive psychotherapy has been indispensable. I attempted to discontinue therapy on several occasions but considerable anxiety developed, and after a few weeks she would return. She was tried on a considerable number of drugs including Tofranil, Catron, Marplan and two of the phenothiazines (Stelazine and Thorazine), without effect. Librium, 10 mg. t.i.d., was administered initially and increased to 60 mg. daily, and she is still on this dosage. Improvement has in the main been steady and progressive. Sleep has become normal, the depression is considerably improved and she now stays alone for progressively longer periods of time. When psychotherapy was terminated, 3 months ago, the patient was driving her car fairly freely, had taken on many new activities, and was able to stay home alone a good part of the time. I continue to see her at monthly intervals. This patient had a borderline condition which was diagnosed as pseudoneurotic schizophrenia.

The second patient was a 53-year-old man who was discharged by his brother from a position he had occupied for 18 years. This began a depression which lasted almost a year before he saw me. This was a fairly typical agitated depression with the usual diurnal variation, insomnia, ideas of guilt, and self-condemnation. He was placed on Tofranil at first, but because of the side effects he discontinued it spontaneously after one day. Librium 10 mg. 3 times daily was then given and he began to improve immediately. I saw him once more a week later at which time he was considerably improved. There was a phone call a week later and at this time he had resumed work, was feeling well and was apparently asymptomatic. Another call a month later indicated that his improvement had been maintained.

In 6 other patients, 3 of whom had borderline states, one an alcoholic and 2 psychoneurotic (one with phobic symptoms) all showed equivocal results. However, there were certain groups of symptoms which showed some amelioration in almost all. Most of the patients showed withdrawal in some form, secondary to symptoms such as anxiety and depression. During Librium therapy most of the patients became more outgoing, and overt anxiety and associated symptoms such as excitability, heart racing, and restlessness, showed some improvement. There was also some improvement in those with symptoms of depression. Insomnia was frequently helped. When loss of energy appeared as a symptom it was often alleviated, although it was also mentioned as a side effect by a number of patients who had not noted it previously.

A number of observations were noted

in connection with Librium therapy. In some of the patients there was early improvement of symptoms which gradually recurred with time. When the dosage was increased side effects appeared, particularly drowsiness, resulting in a spontaneous discontinuance of the drug by the patient. All of these patients were working, some in exacting professional positions requiring intellectual work and concentration. It was rather curious that some patients who seemed to obtain a measure of relief, spontaneously dropped or forgot to take their medication. One patient who claimed some relief has not filled a prescription for three weeks. Since the therapist's grading in these cases showed only very mild or no improvement, it may of course have been a placebo effect. Two of the patients used it only during periods of acute anxiety. One of them continues to use it in this way, and takes it once or twice a week. One patient stated that under the influence of the drug his depression increased, although his anxiety was relieved to some extent.

The side effects consisted mostly of drowsiness, apathy and lack of energy, and these occurred to some extent in most of the patients. One complained of restlessness and one of rash and dryness of the skin, which however, did not necessitate discontinuance of treatment. Two patients complained of decrease in sexual activity. All of these side effects, except for the increase of depression along with relief of anxiety, have been reported in the literature. In addition, dissociative reactions, constipation and acute rage reactions have been reported especially in psychotic patients. Tobin and Lewis reported about 25% of side effects, and they used doses up to 175 mg. daily. Most of our patients had some side effects as noted in the psychotherapeutic sessions and in the drug study inventories. Walzer[17] reported sensitivity to alcohol induced by the drug. There has been no indication thus far of any addicting properties of Librium. The most serious complication[19] reported has been the onset of a granulocytopenia of 1,600 white blood cells/cu. mm. in one patient (previously on chlorpromazine), after one month of Librium therapy in a dose of 40 mg. daily.

Dosage has not been fully determined as yet. Reports have indicated amounts varying from 10 mg. daily to 450, with the usual ranges from 40 mg. to 75 mg. daily. With the upper ranges the side effects increase in frequency. The optimal doses for the various psychiatric categories and symptom complexes need to be further clarified. From our experience in intensive psychotherapy it has been noted that some decrease in concentration and acuity of thought occurs, even with moderate doses, in patients required to do fine intellectual work.

In assessing our results it is important to note that psychotherapeutic work was the main focus of activity; in most patients the drug was secondary to the main psychotherapeutic goal, and so understood. Furthermore in some of these patients, psychoanalytic treatment of a reconstructive type was in process and drug administration was a brief and incidental factor. Accordingly, the expectations of the patient were not as great as in situations where the drug is the main focus of therapeutic activity. For example, one of the patients after a period of time on Librium, mentioned that he would have discontinued it except that he felt that the therapist had given him an unspoken command to continue. Another patient took the medication as a transference weapon, saying that it was the medication which brought about his improvement rather than the psychotherapeutic work. He may have been right, although when the drug was given again at a later time, no effects were noted. The conservative or perhaps even cautious attitude of the therapist towards drugs may unwittingly also have been a factor influencing the patient.

Some of the patients' comments during

associations are of interest with respect to the influence of the drug on psychotherapeutic work. One patient for example said, "I still have ups and downs, but it reduces the amplitude of my cycles. It is more in a straight line though I haven't recovered. I am not so depressed or shaky and can try and do something." Again, "There is a lack of clarity. I have to analyze especially carefully now." Another patient says, "I don't feel I care about things, although I know I do. I just feel it is no use getting upset. I can't do any more than I am doing now." Again, "My pushing, driving attitude is changing. Is it the drug or is it a real change?" From a physician comes this statement, "The drug interferes with my thinking, and my working in treatment, but it blocks the acute depression." The same patient said, "I know the medication is interfering with therapy, but I feel optimistic nevertheless." One patient referred to the medication as "a splint." The same patient spoke of the feelings of "a subjective block as well as objective." "I guess I can tell when I'm taking too much."

There was no increase in the recollection of memories of traumatic experience, and abreaction was not especially apparent with the use of Librium. Sometimes after a period in which anxiety abated, there was a subjective feeling of being "blocked" which was also noted by the therapist. It appeared also that the patient more readily evaded traumatic subjects and skirted painful problems rather than cope with them. When this was brought to their attention they would make the attempt to work with problems, but again diverge to some other topic, much as they do with ordinary resistances, but to a greater extent. It was therefore felt that the resistances were increased by the medication. It was apparent, however, that in patients with acute disabling anxiety, whether precipitated by external events or by the psychotherapeutic work itself, Librium permitted this work to proceed, without the use of complicating procedures such as suspension of occupation, involvement of members of the family, etc. This is also true of severe guilt feelings and depression which so often stultify psychotherapy and lead to its suspension. Librium, accordingly, has been a useful adjunct in intensive psychotherapy. In such cases, however, it should be discontinued when it has served its purpose, and its meaning to the patient should be analyzed.

There seem to be three principal symptomatic effects of Librium: the anti-depressant, the anti-anxiety and the sedative. The site of action of the drug producing these effects is as yet unknown, and only crude judgments are possible, based on criteria of behavioral change. The question of specificity of effects also awaits further study and clarification.

Statistical studies without adequate controls must be regarded with a great deal of caution. DiMascio and Klerman[20] have studied the role of non-drug factors operating during drug administration and emphasize the extreme complexity in evaluating drug effects. Factors in the subject to be evaluated include constitution and physiology, motivation, personality patterns, ego strength and expectations of drug action. Factors in the investigator are equally important: his attitudes and expectations, his orientation or bias, and his transmission of these to the subject. The environment influences drug effects, for example, whether the drug is taken in a group or in isolation, and whether there is a group process at work. The response to drugs will be different if there is a pre-existing relationship between investigator and subject. The initial structuring of the situation and the type of explanations to the patient may produce variation in results. All these operative variables must be considered in any research design, even though an attempt to keep them all as constants may impose insuperable technical difficulties.[21] Disregard of such factors, however, often leads to the "discovery" of miracle drugs and proce-

dures, which after a few years are quietly dropped.

It should be remembered that drug therapy exerts its effect through the blood or cerebrospinal fluid, and psychotherapy including psychoanalysis acts primarily through sensory receptors.[22] It is inconceivable then, for a drug to create new behavior or thought patterns on the psychic apparatus, whereas this is the legitimate goal of psychotherapy. The drug may, however, affect pathways, efferent and afferent, and central processes, and thereby alter the pattern of energy distribution. Accordingly, more adequate utilization of information already acquired, may be made possible.

A satisfactory method of studying the effects of drugs lies in the classical psychoanalytic process, where countertransference effects are at a minimum and subtle changes in the subject can be perceived. Nevertheless, human behavior has so many variables, that no adequate methodology has been worked out for the optimal use of the psychoanalytic method in investigative work. It has been more fruitful in the development rather than in the testing of hypotheses.[23]

Effects of Drugs on the Psychic Apparatus

A discussion of the factors involved in the use of drugs that affect mental functioning should include the psychodynamic, psychoanalytic and sociological aspects of the subject. Several multi-disciplinary works on this topic have been published,[22,24,25] in recent years. However, a brief statement of a conceptual model may help in visualizing the multiplicity of drug effects on the psychic apparatus. Through metapsychological theory, psychoanalysis has given us a framework which may serve to explain or illustrate some of the facts and theories concerning the effects of drugs on mental functioning. The description of the dynamic, economic and structural aspects of human behavior can be illustrated through the use of the tripartite model.[26] Such a conceptual model may be helpful, and Freud's division of the psychic apparatus into id, ego and super-ego, remains the most frequently used model. Here we have a difficulty at the outset, because these are psychological constructs which have proven helpful in understanding intrapsychic events and relationships, but without a physiological or anatomical basis. There is no anatomy of the super-ego, only an anatomy of nervous tissue. These constructs, however, represent certain functions and certain interactions on a psychological or symbolic level, and are delicate indices of drug effects through the influence of the latter on function.

We will not delineate the functions of the three portions of the psychic apparatus since these are well known already. The id, as the repository of the drives, impulses or instincts, is assumed to be the source of all psychic energy. Indeed it is the source of the energy of the ego and super-ego as well, although by the time adulthood is reached, the ego and super-ego have become more or less autonomous in energy sources and resources.

Let us assume, although in practice this is not likely to be true, that there is a drug that influences only the id or a part of it, by inhibition. Murderous impulses for example, may be diminished by use of this drug. We can see that if the ego is in conflict with such impulses, their weakening by the drug will lessen the conflict and make the task of the ego in relating to environment much simpler. Anxiety is likely to lessen or disappear. It is true that a sacrifice will be necessary, for the sources of energy will be inhibited. It is likely that less work, creative or otherwise, will be done, and in extreme cases apathy, disinterest and absence of drive, will occur. On the other hand, if there should be a deficiency of id drives, conceivably a drug might be useful as a stimulant. Here one must be wary of a simultaneous stimulation of defenses, if these drives are condemned by the rest of the

psychic apparatus. An apathetic or depressed patient, however, might be influenced to a better adjustment to his environment.

Now let us assume that we have a drug with its principal effect on the functions of the super-ego, either augmenting or inhibiting its psychic energies. We have reason to believe from psychoanalytic knowledge that in a depression, the super-ego attacks the ego (to anthropomorphize a construct), which results in ideas of guilt and worthlessness. A drug inhibitory to super-ego forces then might change the relative balance of forces and thus free the ego from this burden. Functionally, the anti-depressant drugs modify behavior in this way. Conversely, in the manic attack, the id and ego "triumph" over the super-ego, and we note that excessive doses of the anti-depressants may precipitate a manic phase.

The very complex construct, the ego, is the executor of the psychic apparatus. Receiving messages as it does, from internal sources as the super-ego and id, as well as through perceptions from the environment, it attempts to make a compromise between all these demands. The effects of drugs on the ego are therefore very complex. A prominent example of a drug affecting ego functions especially, is the sedative drug. The ego is inhibited and its contact with the environment lessened, thus relieving the ego of the burden of adjusting to demands of the environment. At the same time inner perceptions are diminished, further decreasing the need for adjustment, although in lower dosages eruption of drives may be permitted as the inhibitory functions of the ego are paralyzed. In the process described, there is a "regression" of the ego, always in a sense pathological, but also permitting the ego period of rest and relief of tensions.

The perceptual functions of the ego are particularly sensitive to drug effects, and it is on the percepts of the ego that the integrative functions are ultimately based. Altering one or more of these functions may produce profound effects of the organism as in the administration of lysergic acid diethylamide. Here we have a situation in which a part of the ego is unaffected and can observe another part whose function is distorted. Interference with the ego by drugs alters the defensive functions and may promote a new balance between drives and defenses. It is conceivable that drugs may be found which affect one or only a few of the ego functions.

Finally, we can consider elimination of the environment. As one investigator put it, this would involve giving drugs to every one but the patient, not a particularly feasible procedure. Removing environmental strain, however, was the basis of the Weir Mitchell cure of the latter part of the last century, where almost total rest was given. Such a procedure is similar to the artificial regression induced by drugs, decreasing stimulation and output of energy. This may permit a realignment of forces which may be therapeutic.

This oversimplified description does not do justice to the infinite complexities induced by a drug in the energies, structure and function of the psychic apparatus. Painstaking observations in separate areas are necessary over a prolonged period of time to elucidate these factors, and fortunately more and more investigators are devoting themselves to this task.

Drugs and Psychotherapy

The focus of therapeutic activity is most often on anxiety and its derivatives, such as guilt. This may be overt, concealed in symptoms or "congealed" in character traits. Drugs may influence both directly perceived or unconscious anxiety. They may be utilized in many ways, depending on the type of patient, the orientation of the therapist, and the therapeutic goals. Pharmacological agents alone are properly used where psychotherapy is not indicated, not available, or not

acceptable to the patient, and need no apology. Patients in certain categories have been helped solely through the use of drugs, and there is no need to label them as "facilitators" of psychotherapy. Skills in the proper selection, timing and dosage of drugs have often been neglected by psychotherapists who may have a "holier-than-thou" attitude to the use of psychopharmacological agents. We require not only analysis of the effects of drugs, but also an understanding of the indiscriminate user of drugs and the inflexible non-user. It may reveal a lack of skill in psychotherapy on one hand, or a rigid devotion to theoretical concepts on the other, often to the detriment of the patient.

The use of drugs in my experience has been helpful in many cases, but has required a certain price. In intensive psychotherapy for example, it may be necessary for the relief of acute disabling anxiety, but often reduces the capacity of the ego to deal with problems in psychotherapeutic work.

If we take a rough average of the 18 studies referred to above, since the figures are not fully comparable, we find that 55.3% of patients (range 20 to 95%) show the top grades of improvement and 75.6% (range 30 to 100%) show a minimal or greater measure of improvement. If placebos produce definite improvement in 35% (Beecher[27]) these figures should be meaningful although we must consider them only as pilot studies. Control studies, however, show an improvement rate of 41.5%.

In summary, chlordiazepoxide (Librium) is a new, interesting and promising drug. The studies, thus far have been mainly in the nature of pilot studies, and investigation of this drug should be continued to establish indications and contraindications, optimal dosage ranges, side effects and complications. Many more controlled, double-blind investigations are essential to demonstrate the validity of the many claims made. The relation of the use of Librium to psychotherapy is an important field of study which should receive considerably more attention. Emphasis thus far has been placed on Librium as a broad spectrum psychopharmacologic agent with effects on symptom complexes rather than diagnostic categories.

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GENERAL DISCUSSION

AFTERNOON SESSION

Q. How long, Dr. Grayson, do you think it would take, following all the criteria that you mentioned, for one to get a drug like Librium evaluated? I am not going to be around thirty years from now. Would Librium have been made available in the next twenty-five years if all that you recommend is done?

Dr. Grayson: Sometimes, we simply have to bide our time until adequate studies are performed. I do not believe it is necessary to take the kind of time you are talking about to do certain kinds of controlled studies which will provide scientific information. I would not come to a final conclusion on the basis of one controlled study; different controlled studies will differ as to findings because different kinds of patients, different dosages, or different evaluative procedures, were used. I believe that if a number of studies were undertaken at this time—controlled studies—in a matter of two years adequate results should be available.

Q. *Dr. Ditman:* Dr. Grayson, in your opinion are there any drugs for which there have been adequate, controlled studies that would conclusively show their value in psychiatry?

Dr. Grayson: Yes. The Veterans Administration has conducted, on a large scale, double-blind controlled studies involving the use of various phenothiazine compounds, disguised and inert placebos, and utilizing very carefully developed evaluative criteria, found that at least some phenothiazines were clearly differentiated from placebo in terms of effectiveness. Incidentally, this does not mean that because a phenothiazine drug is effective, all phenothiazines are because, for example, they found that four were more effective than phenobarbital, a disguised placebo producing side reactions, and an inert placebo, but that a fifth phenothiazine was no more effective than phenobarbital.

Dr. Sidney Cohen: What Dr. Grayson has just said then, is that the exploratory studies —"dirty" studies (that were done during the years before the V.A. started doing "clean" studies) are confirmed. I told Dr. Grayson, many years ago, that Thorazine, Compazine, Vesprin, Stelazine were good drugs for chronic schizophrenic patients, and that Pacatal and phenobarbital were inferior drugs; this is just what the V.A. study showed. My declaration to him was on the basis of "dirty" studies. A "dirty" study can be valuable, gentlemen. I would rather see a "dirty" study by Fritz Freyhan than a clean, double-blind study by many other individuals.

Dr. Grayson: I would like to reiterate that exploratory studies are important, for many reasons. Some which show good results will be supported in more definitely controlled, confirmatory-type studies, and others will not be supported. The very fact that some uncontrolled studies of drugs are substantiated does not necessarily prove that uncontrolled studies can be taken at face value at all times.

The final stage of verification still involves a confirmatory controlled type of research, and this is the point to keep in mind.

The exploratory researches give us leads; sometimes they stand up; sometimes they do not.

Q. *Dr. Nagy:* I want to ask Dr. Mooney about the injection of Librium. At what speed, or rate did you inject 100 mg. of Librium?

Dr. Mooney: I did not do that work; that was done by Ticktin and Schultz, and they did not say in their article.

Dr. Hines: In the Ticktin and Schultz study Librium, 100 mg., was given over a period of about two or three minutes. Since that time, and contrary to our recommendations, a number of people have been giving 100 mg. in 5 cc., and are injecting it substantially more rapidly. I think it should be given over about a 2-minute period. The 5 cc. dilution is all right.

Dr. Lieberman: One thing that impressed me is the fact that the drug is reasonably safe. In the large doses that have been reported here, the individuals did not suffer more than a little hangover and recovered with no ill effects.

Dr. Hayman: The difficulty in psychotherapeutic work is to know exactly what is going on in the patient, to tell what happens in a psychotherapeutic interview; and if you add drugs to it, it is still more difficult. I do not think that as yet we have any research design that is adequate for this.

Q. *Dr. Mandel:* I would like to ask if this is the first of a series of drugs of this class.

Dr. Randall: We have a lot of interesting analogs coming along.

Q. *From the Floor:* I would like to ask Dr. Mooney if he has anything at all to say about the treatment in alcoholism.

From the Floor: At the City Clinic, in alcoholics a patient will begin to ventilate to an extent you have not been able to get out in months with intravenous Ritalin.

Q. *Dr. Mooney:* As I understand it, that is to facilitate psychotherapy, is that right?

From the Floor: Yes.

Q. *Dr. Mooney:* And not in the intoxicated alcoholic?

From the Floor: No.

Dr. Mooney: I have not had any experience with that myself. I have read articles in which those claims were made.

Dr. Ditman: May I answer that? There are reports that Ritalin facilitates ventilation; and that therefore it facilitates psychotherapy. We have looked at Ritalin briefly. My impression is that alcoholics tend to like it because it is a euphoriant drug. In general, they like all euphoriant drugs, and I am not sure that this is not the reason why they come back for Librium, as Dr. Mooney has shown they do. To say that it does them any good, that it improves their alcoholism, I do not have any reason to believe that it does.

Dr. Ditman: Briefly in conclusion let me say that Librium is an interesting compound for which there are some interesting reports, and further conclusive work seems to be indicated.